DISSERTATION

Comparison of Esmolol bolus with Esmolol infusion in reducing peri-intubation stress response in non cardiac surgical patients: A randomized controlled trial.

This dissertation is in partial fulfilment of the requirement for the

M.D Anaesthesiology (branch X) degree examination of

The Tamil Nadu Dr. M.G.R. Medical University, Chennai

to be conducted in October 2015

CERTIFICATE

This is to certify that this dissertation titled **"**Comparison of Esmolol bolus with Esmolol infusion in reducing peri-intubation stress response in non cardiac surgical patients: A randomized controlled trial**."** is an original research work done by **Dr.ANN SUMIN TOMS** towards partial fulfillment of the requirements for the award of MD Anaesthesiology degree.

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ABSTRACT

TITLE: Comparison of Esmolol bolus with Esmolol infusion in reducing peri-intubation stress response in non cardiac surgical patients: A randomized controlled trial.

DEPARTMENT: Department of Anaesthesiology

NAME OF THE CANDIDATE: Ann Sumin Toms

DESIGNATION: Post graduate registrar.

NAME OF THE GUIDE: Dr. Sathish Kumar Dharmalingam.

KEY WORDS: Esmolol bolus, Esmolol infusion, Peri intubation stress response

AIMS OF THE STUDY: 1. To compare the effects of esmolol bolus versus esmolol infusion in reducing the stress response to intubation. 2. To identify which mode of Esmolol administration (infusion/ bolus) reduces the stress response effectively with the least side effects in patients undergoing non cardiac surgery.

MATERIALS AND METHODS: 92 patients, all of whom were classified under ASA I and II and admitted for non cardiac surgery were randomly allocated into 2 groups. The esmolol bolus group received 1.5mg/kg of esmolol over 30 seconds 3 minutes prior to intubation. The infusion group was given a loading dose of 0.5mg/kg over 30 seconds followed by an infusion of 153µg/kg/min for 6.5 minutes and intubated after 2 minutes of stopping the infusion. The haemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded at the baseline, every minute for 2 minutes pre-intubation and every minute for 5 minutes post-intubation and the values were compared between the two groups. Anaesthesia was

induced with propofol 2mg/kg, fentanyl 2µg/kg and muscle relaxation attained with atracurium 0.5mg/kg supplemented with Isoflurane 2%.

RESULTS: Analysis of the data showed a significant rise in heart rate in the post intubation period with both the groups. Both esmolol bolus and infusion was associated with significant pre-intubation and post-intubation hypotension.

CONCLUSION: The rise in blood pressure following intubation was ablated by both esmolol bolus and infusion, but both bolus and infusion failed to effectively prevent the heart rate response to intubation. Esmolol infusion has better haemodynamic stability than esmolol bolus.

INTRODUCTION

Anaesthetizing a patient by giving general anaesthesia requires special attention with regards to maintaining the airway. Intubating the patient using an endotracheal tube is one of the most favored methods of providing general anaesthesia. It helps in maintaining the airway, providing anaesthetizing gases and for ensuring oxygen delivery along with carbon dioxide removal. However, intubating the patient with an endotracheal tube is not devoid of ill effects.

Direct laryngoscopy and endotracheal intubation frequently causes a cardiovascular stress response characterized by hypertension and tachycardia due to reflex sympathetic stimulation. This response is transient and lasts for less than 10 minutes. It may be well tolerated by a healthy individual but may become hazardous in patients with hypertension, diabetes mellitus, coronary artery disease (CAD), cerebrovascular disease or thyrotoxicosis.(1)

Numerous agents like opioids, calcium channel blockers, beta blockers, magnesium sulphate, local anaesthetics etc have been used to blunt the hemodynamic response to laryngoscopy and intubation. Among the various beta blockers, Esmolol is an attractive option because of its cardio selectivity and ultra-short duration of action.(1) However,

there are only two ways by which Esmolol can be administered, either as a bolus or as an infusion. Although both modes of Esmolol administration have been found to be effective in decreasing the stress response, studies comparing these two methods have been rare.

Here we propose to compare the efficacy of beta blockade with Esmolol bolus versus Esmolol infusion (with loading dose) in reducing the stress response with minimal side effects.

AIMS OF THE STUDY

Primary aim

To compare the effects of esmolol bolus versus esmolol infusion in reducing the stress response to intubation.

Secondary aim

To identify which mode of Esmolol administration (infusion/ bolus) reduces the stress response effectively with the least side effects in patients undergoing non cardiac surgery.

REVIEW OF LITERATURE

GENERAL ANAESTHESIA

General anaesthesia means completely anaesthetizing the individual in order to provide analgesia, amnesia and muscle relaxation. The induction of anaesthesia is by a combination of drugs which include analgesics like injection fentanyl 1-2 microgram/kg, induction agents like injection propofol 2-2.5mg/kg or injection thiopentone the dose of which varies with the age of the individual. The usually used adult dose of thiopentone is 4-5 mg/kg. Commonly used intravenous induction agents are injection ketamine and injection etomidate. The drugs used for induction depends upon the patient characteristics and the type of surgery.

If an endotracheal intubation is planned, a muscle relaxant usually follows the administration of the induction agent. It can either be a depolarizing agent like injection succinyl choline 2 mg/kg or non-depolarizing agents like injection atracurium 0.5mg/kg, injection vecuronium 0.1-0.15 mg/kg or injection rocuronium 1mg/kg. Endotracheal intubation is accomplished at a minute after administration of succinyl choline and rocuronium or at 3 minutes following administration of other muscle relaxants. The endotracheal tube is then secured after confirming its correct position.

Agents that decrease the stress response to intubation is either given 3 minutes prior to endotracheal intubation or is timed based on the peak onset of action of the drug. Anaesthesia is maintained with air/nitrous oxide, oxygen, inhalational agents and top ups of muscle relaxant as and when required.

METHOD OF ENDOTRACHEAL INTUBATION BY DIRECT LARYNGOSCOPY

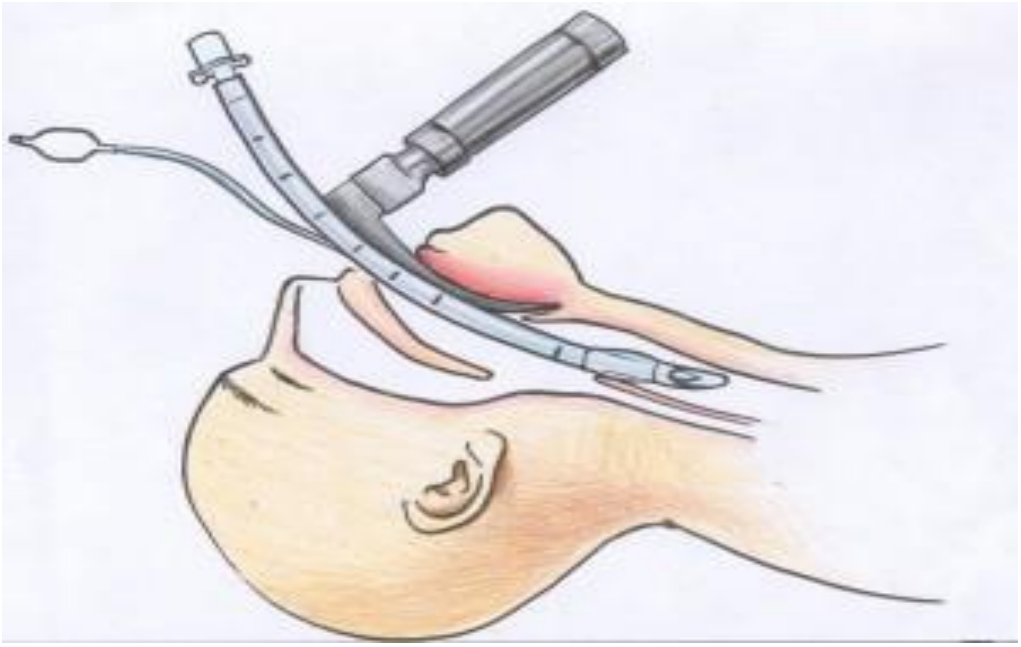


Fig.1: Method of endotracheal intubation by direct laryngoscopy.

The first endotracheal intubation was probably performed by Andreas Vesalius, an anatomist in 1543.(2) William Macewen performed the first orotracheal intubation for

providing anaesthesia in 1878.(3) The first direct laryngoscopy was described by Alfred Kirstein in 1895.(4) However the credit for popularizing endotracheal intubation rests with Edar Rowbotham and Ivan Magill.(5)

The mechanism of endotracheal intubation includes proper positioning of the patient, direct laryngoscopy and insertion of an appropriately sized endotracheal tube. The patient has to be placed in a Magill position which is flexion at the lower cervical vertebra with extension at the atlanto-occipital joint. In the supine position, the oral and pharyngeal axes are perpendicular to each other. Atlanto-occipital extension helps in aligning the oral and pharyngeal axis while flexion of lower cervical vertebra causes the pharyngeal and laryngeal axis to align. In the case of obese patients, ramping is used inorder to bring the oropharyngeal axis in the same plane, wherein the ear lobule and the sternum will be placed at the same level. After fixing the head in this position, the mouth is opened and the laryngoscope is inserted through the side of the mouth. Using the blade of the laryngoscope the tongue is pushed to one side and the blade of scope is brought to the centre. The tip of the laryngoscope blade is then advanced to the vallecula in the case of a curved blade, or beneath the epiglottis in the case of a straight blade. Then pressure is applied to the tip of the blade, in order to lift the epiglottis anteriorly and visualize the glottic opening for inserting the endotracheal tube.(6)

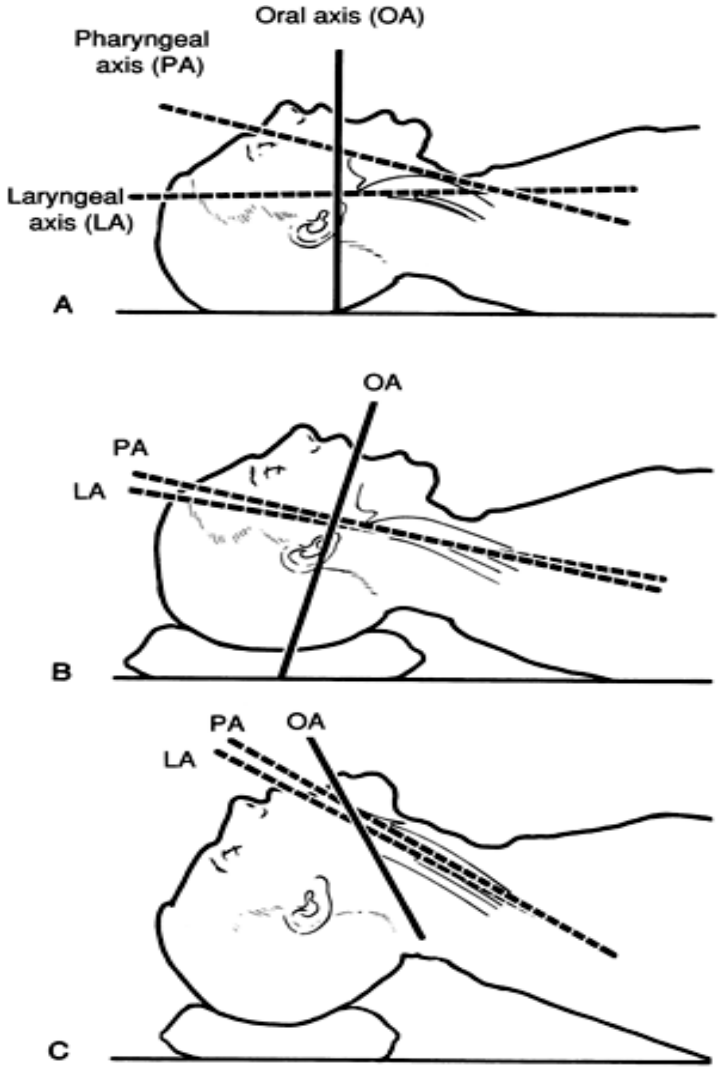


Fig.2: Position for endotracheal intubation.

STRESS RESPONSE TO INTUBATION

Laryngoscopy and endotracheal intubation can alter the haemodynamics of a patient. The first description on the stress response to intubation was given by Reid and Brace.(7) The stress response usually results in sympathetic stimulation, which manifests as an increase in heart rate and blood pressure. Activation of the parasympathetic system can lead to

bradycardia, coughing and bronchoconstriction. These sympathetic and parasympathetic responses to intubation are mediated by the glossopharyngeal and vagus nerves.(8)

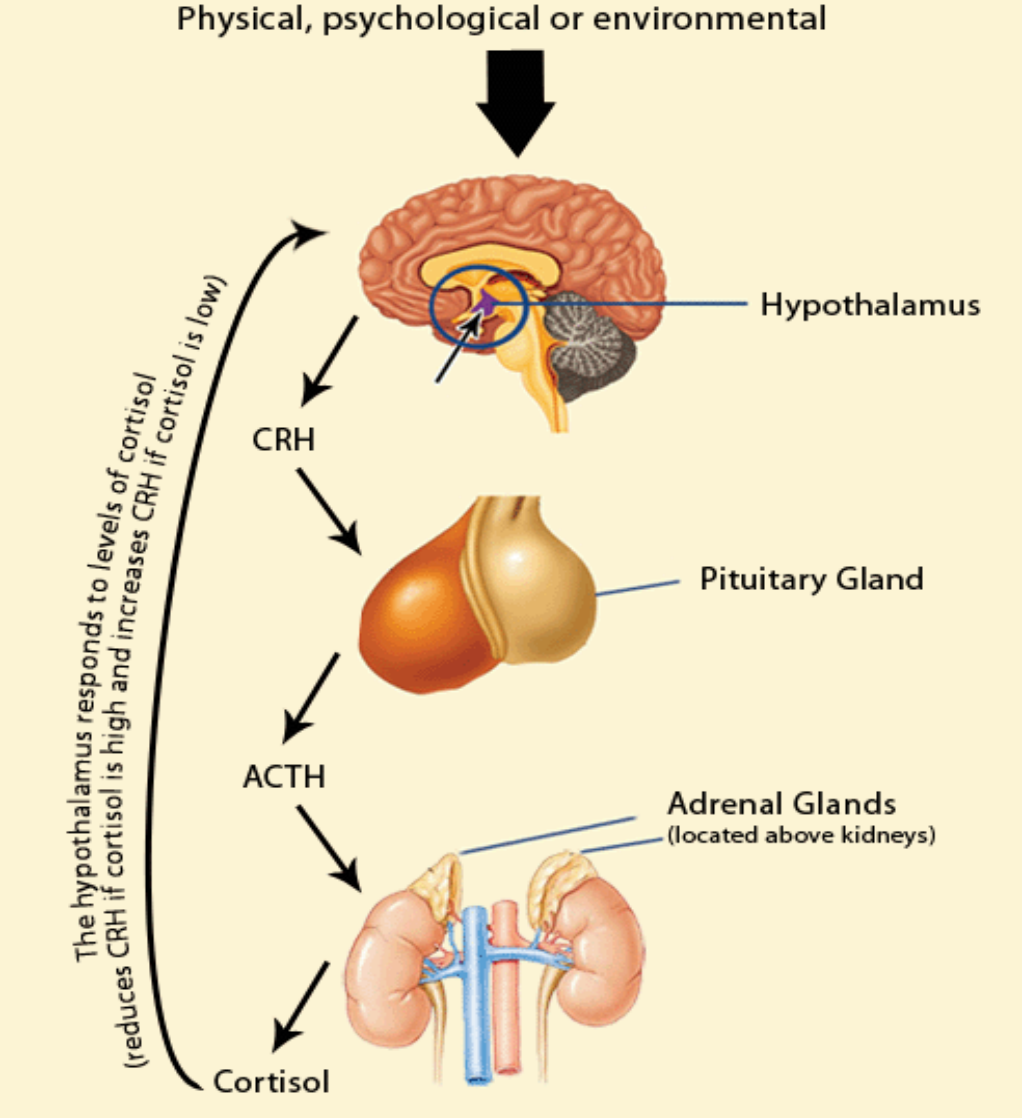


Fig.3: Response to various types of stress in the body.

PATHWAY OF STRESS RESPONSE TO INTUBATION

NERVE SUPPLY OF PHARYNX

Sensory supply to the posterior one third of tongue, the fauces, the tonsils, the anterior epiglottis and the whole of pharynx is by the glossopharyngeal nerve.

Motor supply is provided by the vagus nerve.

NERVE SUPPLY OF LARYNX

Sensory supply: The internal laryngeal nerve which is a branch of superior laryngeal nerve which in turn is a branch of vagus provides sensory supply to the posterior part of epiglottis till the level of the vocal cords. The recurrent laryngeal nerve which is a direct branch of the vagus provides sensory supply to the laryngeal mucosa below the level of the vocal cords.

Motor supply: All the intrinsic muscles of larynx except the cricothyroid are supplied by the recurrent laryngeal nerve. The external laryngeal nerve which is a branch of the superior laryngeal nerve supplies the cricothyroid muscle.(9)

ANATOMY OF THE PHARYNX AND LARYNX

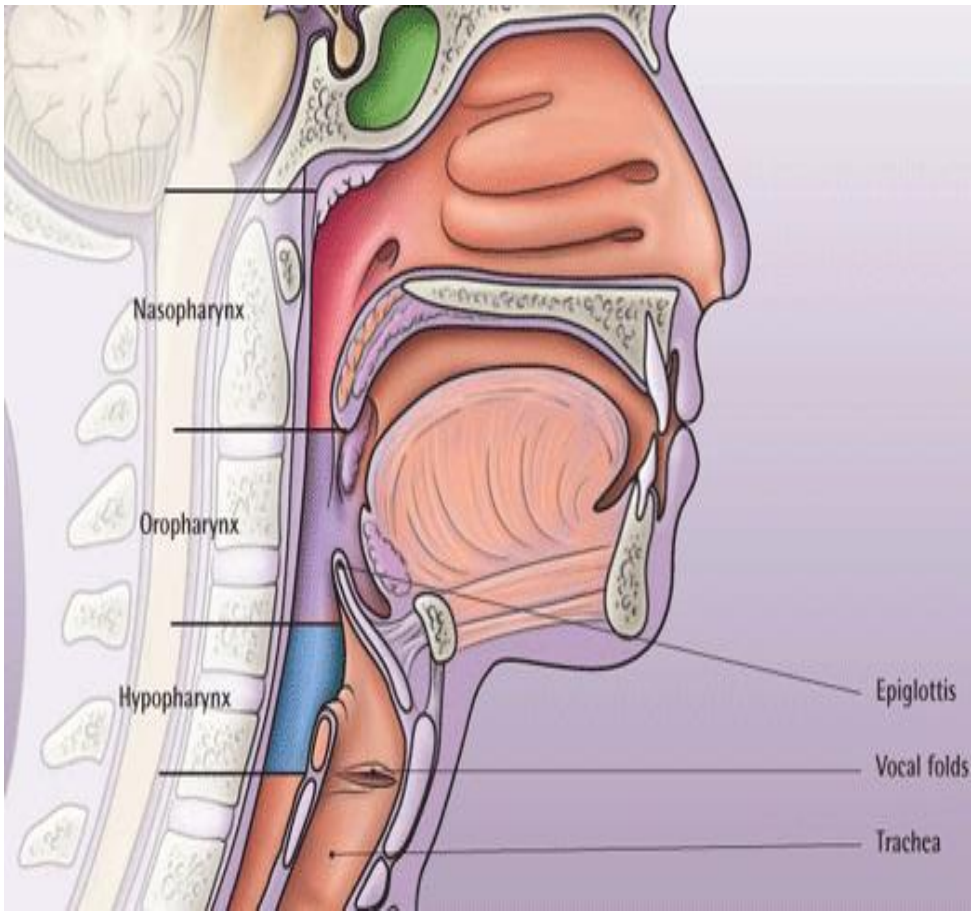


Fig.4: Anatomy of the pharynx and larynx.

REFLEX PATHWAY OF STRESS RESPONSE TO INTUBATION

The sensory information from the hard palate, upper part of the oropharynx, posterior most part of the tongue, lower part of the oropharynx, larynx and trachea are carried by the glossopharyngeal and the vagus nerves. The afferents from these two sensory nerves terminate in the nucleus tractus solitarius.

The fibers from nucleus tractus solitarius terminate mainly in the parabrachial nucleus, which thus becomes the main relay station. The parabrachial nucleus has a minimum of thirteen separate sub-nuclei which projects extensively to many areas of the brainstem, basal forebrain, hypothalamus, cerebral cortex and thalamus. These brain structures are also innervated by direct projections from the nucleus tractus solitarius.

The principal sites for the integration of function of the autonomic nervous system are the hypothalamus and the nucleus tractus solitarius. It includes regulation of fat and carbohydrate metabolism, water balance, body temperature, emotions, blood pressure, respiration, sleep and reproduction. Stimulation of the hypothalamus and nucleus tractus solitarius results in release of hormones and activation of the bulbospinal pathways, which in turn mediates motor and autonomic responses.(10)

PHASES OF STRESS RESPONSE TO INTUBATION

Stress response to intubation can be divided into two phases. Phase one occurs during laryngoscopy due to stretching of the pharyngeal muscles. Phase two occurs due to stretching of the laryngeal muscles following insertion of the endotracheal tube into the trachea and its inflation. Both phases are associated with stress response but it has been found to be greater in phase two as compared to phase one.(11)

MANIFESTATION OF STRESS RESPONSE TO INTUBATION

Ever since the first description of haemodynamic disturbance occurring due to laryngoscopy and endotracheal intubation was given by Reid and Brace in 1940(7), many other studies have been carried out describing the same. A study by Burstein et al have shown that endotracheal intubation is accompanied by ECG changes in as much as 68% of the cases.(12) King et al described in his study that insertion of an endotracheal tube into the trachea augments the haemodynamic stress response caused by laryngoscopy, in addition to producing cardiac arrhythmias.(13)

Stress response to laryngoscopy and endotracheal intubation may manifest as a sympathetic or a parasympathetic response.(8) The sympathetic response raises the plasma catecholamine levels, with a subsequent increase in heart rate and blood pressure. Direct laryngoscopy and endotracheal intubation can result in an average of 40-50% increase in blood pressure and about 20% increase in heart rate. (14) This increase in heart rate and blood pressure in turn can cause myocardial ischemia, myocardial infarction, cardiac arrhythmias, acute heart failure, pulmonary oedema and raised intracranial pressure. The raised intracranial pressure can be hazardous in patients with intracranial tumours and cerebral aneurysms. It can even cause rupture of an intracranial aneurysm.(15,16).

Endotracheal intubation can also cause a rise in intraocular pressure.(17) Increased activity of the sympathetic nervous system in hypertensive patients (15) results in them

showing an exaggerated and unpredictable sympathetic response to laryngoscopy.(16) The haemodynamic response to intubation is maintained at a high level in patients with both treated and untreated hypertension.(18) The activation of the parasympathetic system can lead on to bradycardia, coughing and bronchoconstriction.(8) This stress response to endotracheal intubation is a transient one which starts with laryngoscopy and lasts for about 5-10 minutes following intubation.(15)

Direct laryngoscopy and tracheal intubation is considered as the most critical event in the administration of general anaesthesia due to its propensity to produce a marked but transient sympatho-adrenal response.(19)

FACTORS AFFECTING STRESS RESPONSE TO INTUBATION

a. Duration of laryngoscopy:

The stress response to intubation increases with the duration of laryngoscopy.(20) The magnitude and duration of the haemodynamic changes will be less if the duration of laryngoscopy is kept to less than 15 seconds.

b. Plane of anaesthesia:

Intubation response will be more if the plane of anaesthesia is light.(21, 22)

c. Number of intubation attempts:

Repeated intubation attempts causes the stress response to increase.(16)

d. Type of intubation equipment:

Recent advances in the field of anaesthesia have resulted in the invention of new equipments and in the modification of older equipments. This has made intubation easy even under trying circumstances. Many studies have been carried out to find whether there is a difference in stress response to intubation with the use of these newer equipments.

Haidry et al compared the stress response to intubation with McCoy and Macintosh laryngoscopes. The changes in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were compared for 10 minutes after intubation. They concluded that the haemodynamic changes were of a shorter duration and of a lesser magnitude with McCoy laryngoscope when compared to Macintosh laryngoscope.(23)

Ghoneim et al compared between Bonfils intubation endoscope and Macintosh laryngoscope. Based on the changes in heart rate, mean arterial pressure, blood catecholamine levels and intra-ocular pressure in the post intubation period they concluded that Bonfils endoscope is associated with less haemodynamic instability than with Macintosh laryngoscope.(24)

Kitamura et al compared the haemodynamic effects of intubation with a Styletscope and

a Macintosh laryngoscope. Based on the heart rate and blood pressure changes following intubation it was concluded that haemodynamic stability was better with a Styletscope than with a Macintosh laryngoscope.(25)

Similarly various other studies were conducted to compare the stress response to intubation with regards to different anaesthesia equipments. Siddiqui NT et al in their study on ASA I and ASA II patients found that intubation through a intubating laryngeal mask airway was associated with a lesser degree of stress response as opposed to using a Macintosh laryngoscope.(26)

Sener EB et al compared the hemodynamic responses following tracheal intubation with conventional laryngoscopy and intubating laryngeal mask airway in hypertensive patients. Measurement of systolic blood pressure, diastolic blood pressures, heart rate, rate pressure product and ST segment changes were made at baseline, pre intubation, and every minute for the first 5 minutes following intubation. The duration of intubation, number of intubation attempts, and the airway complications were also recorded. The intubation time was seen to be less in the conventional laryngoscopy group as compared to the intubating laryngeal mask airway group. The systolic blood pressure, diastolic blood pressure and the rate pressure product were found to be higher in the intubating laryngeal mask airway group as compared to those in the conventional laryngoscopy group at 1 and 2 minutes following intubation. There were no differences in the ST segment changes between the two groups.

Repeated and intensive oropharyngeal and tracheal stimulation from an intubating laryngeal mask airway induces a greater pressor response when compared to conventional laryngoscopy in hypertensive patients. Hence they concluded that conventional laryngoscopy, which is rapid and safe to perform, may be preferred in hypertensive patients with normal airways.(16) Various studies have also concluded that there is no difference in the intubation response between glidescope, video laryngoscope and direct laryngoscope.(27)

e. Skill of the anaesthesiololgist:

Duration of laryngoscopy and failed attempts are less with a trained anaesthesiologist and thereby the stress response.

f. Co-morbidity

Intubation response has been found to be exaggerated in hypertensive patients.(16)

Various attempts have been made from time to time to decrease or eliminate the sympathetic response to laryngoscopy and endotracheal intubation. Rosenberg and Kuhn used cocaine as a local anaesthetic to prevent the cough reflex during endotracheal intubation.(3) Intravenous injection of procaine prior to endotracheal intubation was found to be worthwhile by some.(28) Adrenergic agents like phentolamine have also been employed to reduce the stress response. It has been shown that 5mg doses of phentolamine effectively obtunds the laryngoscopic response to endotracheal intubation.(29)

Durrani et al compared the effects of preservative free chloroprocaine 4.5mg/kg and lignocaine 1.5mg/kg given intravenously 45 seconds prior to endotracheal intubation. It was seen that chloroprocaine effectively blunted the stress response to laryngoscopy and intubation and had a better haemodynamic stability than 1.5 mg/kg lignocaine.(30)

DRUGS USED IN THE ABLATION OF STRESS RESPONSE TO INTUBATION

A short duration smooth laryngoscopy of less than 15 second duration is the most effective way of decreasing the stress response.

Lignocaine.

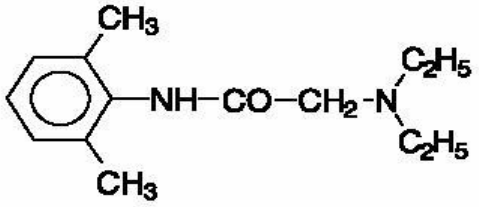


Fig.5: Structure of Lignocaine.

Lignocaine is an amide based local anaesthetic. It acts by selectively binding to sodium channels in its inactive closed state, thereby preventing its change into the activated open state, and thus causing a conduction blockade for nerve impulses. Of the various preparations available, 2% preservative free lignocaine 1.5 mg/kg is used intravenously

90 seconds before tracheal intubation to decrease the stress response associated with intubation.

Lignocaine has a property of increasing the cerebrovascular resistance and thus reducing the cerebral blood flow. This helps in preventing the rise of intracranial pressure that occurs during intubation. In addition, its anti-tussive property while decreasing the reflex induced bronchospasm also accounts for ablation of stress response during intubation. Though effective in decreasing the systemic vascular resistance, it has been found to be ineffective in reducing the heart rate in response to intubation.(31)

In a study, Tajne et al compared magnesium sulphafe 50mg/kg given one minute before the induction of anaesthesia with lignocaine 1.5 mg/kg given 90 seconds before induction in decreasing the haemodynamic response to intubation. He concluded that lignocaine was better in reducing the intubation response whereas magnesium sulphate ablated the hypertensive response alone to laryngoscopy and intubation.(32)

You Mi Ki et al studied the effects of topical lignocaine 4% and 10% sprayed into the larynx after laryngoscopy but before intubation and the subsequent haemodynamic changes that occurred in children aged 2-16 years. They concluded in their study that topical lignocaine spray into the larynx despite the concentration, was ineffective in suppressing the stress response.(33)

Abou M Adi et al compared the effects of different doses of lignocaine- 0.75mg/kg and 1.5mg/kg in blunting the stress response to intubation. It was shown in his study that low

dose lignocaine was ineffective in attenuating the stress response to intubation whereas lignocaine 1.5mg/kg offered borderline protection against post intubation tachycardia and hypertension.(34)

Venus et al tried topical anaesthesia of the oropharynx with 6ml of 4% lignocaine for attenuation of stress response to intubation and concluded that lignocaine aerosolization successfully prevented the increase in heart rate and arterial pressure following endotracheal intubation.(35)

Fentanyl

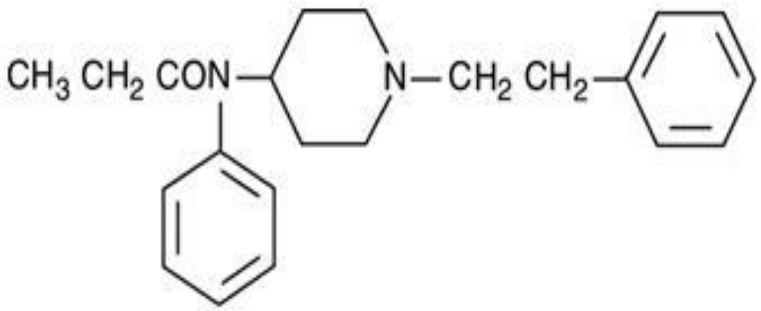


Fig.:6: Structure of Fentanyl.

Fentanyl is a synthetic opioid agonist. It has a rapid onset of action in 1 to 2 minutes and the peak effect is attained in 3 to 5 minutes.It has a short duration of action of 30-60 minutes. After intravenous administration rapid re-distribution of the drug occurs to inactive tissue sites like skeletal muscle, adipose tissue and lungs. The pKa of fentanyl is 8.4. It is 79%- 87% protein bound. Fentanyl is used for ablation of stress response as an

adjuvant to inhalational anaesthetics during intubation at a dose of 2 to 20 microgram per kilogram intravenously. It can also be used for opioid induction of anaesthesia, for premedication as well as intra-operative and post-operative analgesia.

The advantages of using fentanyl as an induction agent include absence of direct myocardial depression, lack of histamine release and ablation of the stress response to intubation and surgery. The disadvantage of fentanyl induction is that, even at any dose it cannot prevent the sympathetic response to a painful surgical stimulus. It is also said to cause intra operative patient awareness. The other concern regarding the use of high dose fentanyl for induction of anaesthesia is the possibility of post operative ventilatory depression.

The common side effects include bradycardia, chest rigidity, seizures on rapid intravenous administration, a modest rise in intracranial pressure and post operative respiratory depression. (31)

Hosalli et al compared the efficacy of different doses of fentanyl in decreasing the stress response to laryngoscopy and endotracheal intubation. They compared fentanyl 3µ/kg with fentanyl 5µ/kg given 3 minutes before endotracheal intubation in ASA 1 and ASA II patients. They concluded that fentanyl 5µg/kg gave better haemodynamic stability when compared to fentanyl 3µ/kg.(36)

Hassani et al compared the effects of fentanyl 2µ/kg with fentanyl 2µg/kg and lignocaine 1.5mg/kg given intravenously 3 minutes before endotracheal intubation in decreasing the

stress response. They found that both fentanyl alone and fentanyl given along with lignocaine could effectively blunt the intubation response to endotracheal intubation. Fentanyl along with lignocaine did not provide any added advantage over fentanyl alone in decreasing the stress response.(37)

Mireskandari et al compared the efficacy of different opioids in attenuating the haemodynamic response to intubation in ASA I and II paediatric patients aging from 1 to 6 years. They compared between intravenous fentanyl 1µ/kg, alfentanil 10µg/kg, sufentanil 0.1µg/kg and remifentanil 1µg/kg. The study drug was given before induction of anaesthesia. Anaesthesia was induced with propofol 2.5mg/kg, and the muscle relaxation achieved with cisatracurium 0.2mg/kg. Endotracheal intubation was done 3 minutes after induction of anaesthesia. It was concluded that intravenous fentanyl achieved better haemodynamic stability when compared to intravenous remifentanil, sufentanil or alfentanil in the above mentioned doses.(38)

Sufentanil

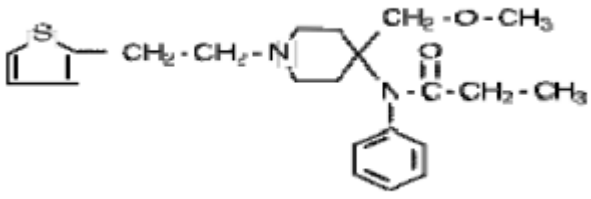


Fig.7: Structure of Sufentanil.

Sufentanil is a highly potent μ opioid receptor agonist. It has a rapid onset of action with peak effect in 3-5 minutes. It is highly protein bound, at about 93% and this contributes to its small volume of distribution. In the body, it is mainly bound to alpha one acid glycoprotein and is metabolized in the liver by N-dealkylation and O-demethylation. The by-product des-methyl sufentanil has 10% activity of the parent compound and is excreted by the kidneys.

It can be used in opioid induction, as an adjunct to total intravenous anaesthesia, to decrease the stress response to intubation and labour analgesia. The complications of sufentanil include bradycardia, rigidity of the chest and abdomen, seizures on rapid intravenous administration and a moderate increase in the intracranial pressure in head injury patients in addition to other opioid side effects. The chest wall rigidity may make ventilation difficult which can be overcome by endotracheal intubation.(31)

Xue et al in his study has compared the effects of intravenous sufentanil at various doses namely 0.1μg/kg, 0.2μg/kg and 0.3μg/kg given 5 minutes before endotracheal intubation along with propofol induction in decreasing the stress response to intubation in paediatric population. They concluded that sufentanil at 0.3μg/kg was most effective in completely abolishing the cardiovascular responses to intubation(39) .

Zsigmond EK et al studied the effects of neuroleptanalgesia with midazolam and fentanyl in decreasing the stress response to tracheal intubation in adult patients undergoing coronary artery surgery. Midazolam was given at a dose of 0.14 +/- 0.01mg/kg over one minute followed by sufentanil 1.5μg/kg 5 minutes later. A total of 4-5μg/kg of sufentanil

was given in incremental doses over 10 minutes before tracheal intubation. Pancuronium 0.1mg/kg was given one minute after the initial dose of sufentanil for providing muscle relaxation. No adverse haemodynamic response or increase in catecholamine levels were seen following tracheal intubation.(40)

Remifentanyl

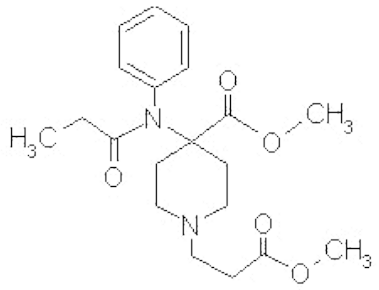


Fig.8: Structure of Remifentanyl.

Remifentanil is a μ opioid receptor agonist. It has a rapid onset of action with peak effect in 3 to 5 minutes.(41) It has a unique structure due to its ester linkage. Steady state plasma concentration is reached 10 minutes after starting an infusion. As a result of rapid clearance and rapid achievement of blood brain equilibration, a change in the rate of infusion will cause immediate changes in the effects produced. The elimination half time for remifentanil is 6.3 minutes. Context sensitive half time for remifentanil is 4 minutes and is not dependent on the duration of infusion of the drug.

Its ester linkage makes it susceptible to metabolism by non specific tissue and plasma esterases. As a result of this esterase metabolism it has a rapid and precise titratable effect, rapid onset and offset of action, and no cumulative effect. The pharmacokinetics of remifentanil is usually not changed in renal or hepatic failure, as the esterases are preserved in these conditions.

Remifentanil is used for providing intra operative and post operative analgesia, induction of anaesthesia along with a hypnotic and to decrease the stress response to laryngoscopy and intubation. The side effects include vomiting, nausea, depression of ventilation, minimal decrease in heart rate and blood pressure, skeletal muscle rigidity on rapid intravenous injection of large bolus doses. (31)

O'Hare et al compared the efficacy of using different bolus doses of remifentanil 0.5µ/kg, 1µg/kg and 1.5µg/kg given over 30 seconds in patients undergoing rapid sequence induction of anaesthesia and noting whether there is a definite reduction of stress response to intubation. They found that 0.5µg/kg was ineffective in blunting the intubation response where as remifentanil at 1.5µg/kg was associated with hypotension. Remifentanil at 1µg/kg abolished the stress response to intubation, albeit with a small increase in diastolic blood pressure.(42)

McAtamney et al compared the effects of remifentanil 0.25µg/kg, 0.5µg/kg and 1µg/kg to decrease stress response to intubation in ASA I and ASA II patients. The study drug was given as a bolus over 30 seconds 1 minute prior to intubation. They concluded that

when compared to remifentanil 0.25µg/kg and 0.5µg/kg, remifentanil 1µg/kg was more effective in decreasing the haemodynamic response to intubation.(43)

Alfentanil

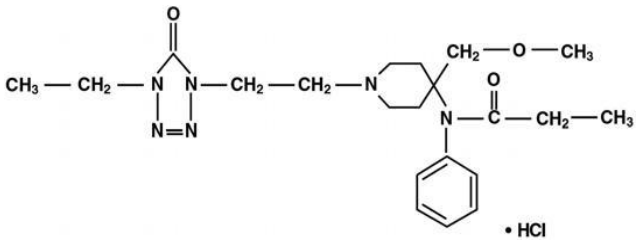


Fig.9: Structure of Alfentanyl.

Alfentanil is a fentanyl analogue which is less potent and with a shorter duration of action as compared to fentanyl. It has a rapid onset of action after intravenous administration when compared to sufentanil and fentanyl. It has a pKa of 6.5 and is 92% protein bound. Alfentanil is mainly bound to the protein alpha one acid glycoprotein. At a pH of 7.4 nearly 90% of the drug exists in the non ionized form. It crosses the placenta as well as the blood brain barrier. Alfentanil is metabolized in the liver. There is no change in the clearance or elimination half time of alfentanil in renal failure. Almost 96% of the drug is eliminated from the circulation within one hour of its administration.

Alfentanil at 15 microgram per kilogram given intravenously 90 seconds prior to direct laryngoscopy can decrease the heart rate and blood pressure response to intubation and laryngoscopy.

Alfentanil like other opioids can cause respiratory depression, pruritus etc. It also increases the pressure in the biliary tract and has the potential for producing acute dystonia in untreated Parkinsons' patients. (31)

Miller et al studied the efficacy of varying bolus doses of alfentanil 15µg/kg, 30µg/kg and 45µg/kg in reducing the haemodynamic stress response to intubation. Alfentanil was administered before the induction of anaesthesia and tracheal intubation done, a minute after the induction of anaesthesia. It was noticed that a dose dependent reduction in catecholamine response was seen till a dose of 30µg/kg of alfentanil was reached. Any further increase in dose did not provide additional advantage.(44)

Martineau et al studied the effects of bolus dose alfentanil 30µg/kg, 45µg/kg and 60µg/kg in reducing the haemodynamic response to rapid-sequence induction of anaesthesia. After administration of the study drug anaesthesia was induced with thiopentone 4 mg/kg and succinyl choline 1.5mg/kg. Trachea was intubated one minute after induction. It was concluded that alfentanil 30µg/kg effectively reduced the tachycardia and hypertensive response to intubation without causing much haemodynamic instability whereas higher doses of alfentanil was associated with a significant but transient decrease in heart rate and mean arterial blood pressure.(45)

Clonidine

Clonidine is a centrally acting sympatholytic with a greater affinity for alpha 2 receptors as compared to alpha 1. The major haemodynamic changes results from the stimulation

of α2A receptors in the medulla. This results in decreased sympathetic nervous system outflow to peripheral tissues from the central nervous system causing a decrease in heart rate, systemic blood pressure and cardiac output. Clonidine is used as an antihypertensive agent, as an analgesic, for treatment of opioid withdrawal, for abatement of shivering, for premedication and for attenuating of the haemodynamic response to laryngoscopy and intubation. Clonidine is used orally or intravenously to decrease the stress response to intubation. While the peak effect of intravenous clonidine is obtained within 10 minutes, it takes about 60-90 minutes for oral clonidine. The most common side effects of clonidine are xerostomia, sedation and rebound hypertension.(31,46)

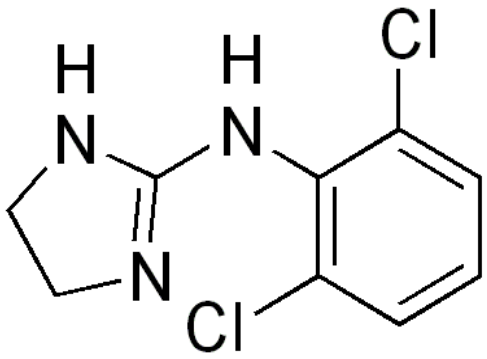


Fig.10: Structure of Clonidine.

Arora et al compared the effects of intravenous clonidine 1µg/kg and 2µg/kg given 10 minutes before induction of anaesthesia in reducing the stress response to laryngoscopy and endotracheal intubation. While fentanyl 2µg/kg/ propofol 1 to 1.5 mg/kg was used for induction of anaesthesia, muscle relaxation was provided for by atracurium 0.6mg/kg. Endotracheal intubation was performed 3 minutes after induction. It was concluded that a single intravenous bolus dose of clonidine 1µg/kg with fentanyl 2µg/kg is a safe method

to decrease the stress response to laryngoscopy without much haemodynamic disturbances. Clonidine 2µg/kg was associated with hypotension at the time of induction and post operative sedation.(47)

Sameenakousar et al compared intravenous clonidine 2µg/kg with fentanyl 2µg/kg given over 30 seconds 5 minutes before laryngoscopy. Anaesthesia was induced with thiopentone 5mg/kg and succinyl choline 2mg/kg. They concluded that intravenous clonidine 2µg/kg was better than fentanyl 2µg/kg in reducing the stress response to laryngoscopy and intubation.(48)

Zalunardo et al compared the efficacy of intravenous clonidine 3µg/kg given immediately before induction and oral clonidine 4µg/kg given 90 minutes prior to induction in decreasing the catecholamine response to endotracheal intubation. They concluded that intravenous clonidine gave much better haemodynamic stability to endotracheal intubation than oral clonidine.(49)

Dexmedetomidine.

Dexmedetomidine is a potent alpha 2 receptor agonist with 1600 times more selective action than alpha 1. The onset of action of dexmedetomidine is within 5 minutes and peak effect is seen in 15 minutes. It is available as a parenteral formula. It is 94% protein bound and the elimination half time of dexmedetomidine is 2 to 3 hours.

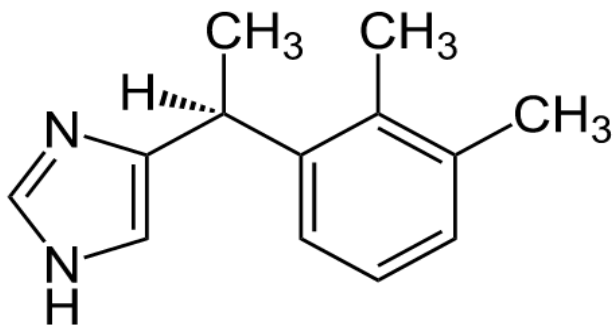


Fig.11: Structure of Dexmedetomidine.

Dexmedetomidine provides sedation, anxiolysis, hypnosis, analgesia and sympatholysis. It decreases intraocular pressure, catacholamine release and peri operative analgesic requirement. It is also useful in decreasing the stress response to intubation and laryngoscopy and for maintanance of anaesthesia. The common side effects seen with dexmedetomidine are hypotension and bradycardia. (50,51)

Gogus et al compared the efficacy of intravenous dexmedetomidine 1µg/kg infusion in 10 minutes with fentanyl 2µg/kg and with esmolol 2 mg/kg given 2 minutes before induction of anaesthesia in decreasing the haemodynamic response to laryngoscopy and intubation. Induction of anaesthesia was done with thiopentone 6mg/kg, with vecuronium 0.1mg/kg providing for muscle relaxation. Tracheal intubation was performed 3 minutes after induction. They concluded that dexmedetomidine was superior in decreasing the tachycardia following tracheal intubation.(52)

Smitha KS et al studied the efficacy of different doses of dexmedetomidine in ablation of sympathetic response to endotracheal intubation. They compared between dexmedetomidine 0.5µg/kg and 1µg/kg given over 10 minutes before endotracheal intubation. Induction of anaesthesia was done with fentanyl 1-2µg/kg and sleep dose of

propofol, with muscle relaxation provided by vecuronium 0.1mm/kg. It was concluded in their study that dexmedetomidine 1µg/kg was more effective in ablation of haemodynamic response to intubation than dexmedetomidine 0.5µg/kg.(20)

Volatile anaesthetics

MAC intubation is the minimum alveolar concentration of inhalational anaesthetic that is necessary to prevent the stress response to endotracheal intubation. Volatile anaesthetics in low concentration (0.6-1MAC) may help prevent the increase in blood pressure following noxious stimuli.

Nitroglycerine

Nitroglycerine is a peripheral vasodilator which acts principally on the veins. It acts by generating nitric oxide which is a potent vasodilator. It has a rapid onset of action with peak effect in 2-5 minutes. The total duration of action is also very short, about 5 to 10 minutes. The elimination half life is 1.5 minutes

It is used in the treatment of angina pectoris as it reduces the preload, afterload and oxygen requirement. It also causes dilatation of coronary blood vessels and redistribution of blood flow to ischemic areas. It is also used in the management of acute hypertension, for providing controlled hypotension, cardiac failure, and to decrease the stress response to laryngoscopy and endotracheal intubation.The commonest side effect is headache. The other side effects are postural hypotension, meth-hemoglobulinemia, tachycardia, nausea, vomiting, giddiness, intolerance and chest discomfort. (31,53)

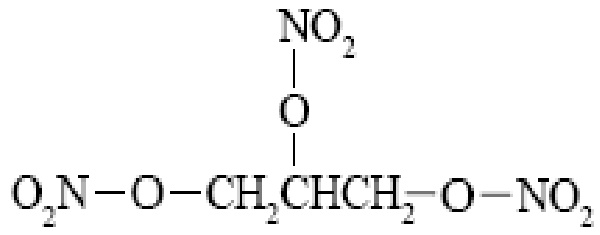


Fig.12: Structure of Nitroglycerine.

Safavi et al compared the efficacy of intravenous nitroglycerine 5µg/min given as infusion with the same repeat dose every 5 minutes till the systolic blood pressure was between 120 to140mmHg, with intravenous hydralazine 5mg initially and further doses of 10 mg as per the recommendations of American College of Obstetrics and Gynaecology and with sublingual nifidipine 10mg in patients with pre-eclampsia. The study drug was administered after 5 minutes of pre-oxygenation. Anaesthesia was induced with thiopentone 5mg/kg and tracheal intubation was performed 1 minute after

intravenous administration of succinyl choline 1.5mg/kg. It was concluded that intravenous nitroglycerine attenuated the haemodynamic effects of intubation better than intravenous hydralazine or sublingual nifedipine.(54)

Sodium nitroprusside

It is a non selective directly acting peripheral vasodilator. It has an immediate onset and short duration of action. It acts via the formation of nitric oxide. It is used for hypertensive emergencies, for providing controlled hypotension during anaesthesia and surgery, in acute and chronic heart failure, in the surgery for pheochromocytoma, in cardiac surgeries that requires bypass, to decrease transfusion need and to decrease the stress response to laryngoscopy and intubation with a dose of 1–2 microgram/kg rapid I.V prior to intubation.

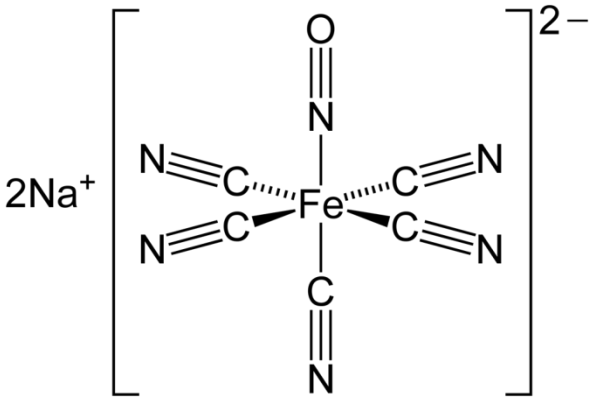


Fig.13: Structure of Sodium nitroprusside.

Its side effects include bradyarrythmias, tachyarrythmias, hypotension, raised intracranial pressure, metabolic acidosis, methhaemoglobulinemia, cyanide poisoning and thiocyanate toxicity.(31)

Labetalol

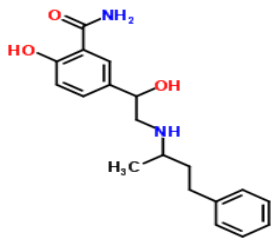


Fig.14: Structure of Labetalol.

Labetolol is an alpha and beta receptor antagonist. It acts on alpha 1, beta 1 and beta 2 receptors. While oral labetalol has a 3:1 beta to alpha blocking potency, it is 7:1 beta to alpha receptor blockade for intravenous labetolol.

Labetalol is used in the management of hypertensive emergencies, angina pectoris and for providing hypotensive anaesthesia. Intravenous labetalol 0.1-0.5 mg/kg 5 minutes before intubation decreases the stress response to laryngoscopy and intubation. (31)

Inada et al compared the efficacy of intravenous lignocaine 100mg with labetalol 5mg and with labetalol 10mg given 2 minutes before tracheal intubation. They concluded that the hypertensive response was similar in all groups, with labetalol 10mg being better in controlling tachycardia.(55)

Chung et al studied the effects of intravenous labetalol on haemodynamic stress response at a dose of 0.4mg/kg given 5 minutes before endotracheal intubation. It was shown that the heart rate response to endotracheal intubation was effectively decreased by labetalol, but its effect on blood pressure was minimal.(56)

Calcium channel blockers

Various calcium channel blockers have been tried in reducing the intubation stress response.

a. Nicardipine

Mikawa et al compared the efficacy of varying doses of nicardipine 15µg/kg and 30µg/kg in attenuating the cardiovascular response to intubation when given 60 seconds prior to laryngoscopy. They found that in both groups nicardipine decreased the rise in rate pressure product and mean arterial pressure following intubation.(57)

b. Verapamil

Yaku et al studied the effects of verapamil on stress response to intubation. The study drug was administered at either 0.05mg/kg or 0.1mg/kg and was given 45 seconds prior to intubation. It was further compared with a saline group. It was found that the rise in mean arterial pressure was significantly lower in patients treated with verapamil although it failed to ablate the rise in heart rate following intubation.(58)

Mikawa et al compared between the various calcium channel blockers. 60 normotensive patients undergoing rapid sequence induction were selected for the study and were divided into 4 groups. Each group received either saline, nicardipine 30µg/kg/min, verapamil 0.1mg/kg or diltiazem 0.2mg/kg. While verapamil was given 45 seconds prior to intubation, other drugs were administered 60 seconds prior. The rise in arterial pressure following intubation was reduced by all calcium channel blockers, with verapamil attenuating the heart rate response when compared to other calcium channel blockers.(59)

Newer calcium channel blockers like nilvadipine have also been tried for decreasing the stress response to intubation.(60)

Other drugs

Other drugs that have been tried for decreasing the stress response to intubation includes magnesium sulphate(61), ganglion blockers like trimethaphan(62), adenosine triphosphate(63), pindolol(64), diazoxide(65), mexiletine(66) and manidipine(67) to name a few.

In recent times various modalities have been employed to modify the stress response that occurs with laryngoscopy and endotracheal intubation. It has been either by the usage of premedication, deepening the plane of anaesthesia, use of ganglion blockers, or by the use of drugs like sodium nitroprusside, nitrogylecerine , calcium channel blockers , intravenous lignocaine to name a few. (68) But these modalities have had their own

limitations. While the use of calcium channel blockers resulted in reflex tachycardia, sodium nitroprusside/ nitroglycerine required invasive monitoring, and lignocaine gave inconsistent results. Recently, esmolol a short acting beta blocker was found to be extremely effective in decreasing the stress response. The efficacy of esmolol bolus in decreasing intra-operative tachycardia has been well documented in recent studies. (69)

Esmolol

Esmolol is a short acting cardio-selective beta blocker. It can be used as both bolus and infusion. In bolus dosing, esmolol at a dosage of 1.5 mg / kg over 30 seconds 3 minutes prior to laryngoscopy and endotracheal intubation effectively decreases the stress response to intubation.(1) In infusion dosing, continuous infusion of esmolol 50 to 300 microgram / kg / minute following an initial bolus of 0.5 mg/kg over 30 seconds is also effective in decreasing the stress response. (6)

Molecular basis of beta receptor function

All adrenergic receptors are G protein coupled receptors that link to heterotrimeric G proteins. Beta receptor has preference for Gs receptor. The response due to activation of beta receptor occurs because of effects mediated by G protein on second messenger generation and ion channel activity.

Structure of beta receptor

Adrenergic receptors constitute a family of closely related proteins that are functionally and structurally related to G protein coupled receptors. Membrane spanning regions are crucially involved in ligand binding. These regions appear to create a ligand binding pocket analogous to that formed by the membrane spanning regions of rhodopsin to accommodate the covalently attached chronophore, with molecular models placing catecholamines either horizontally or perpendicularly.(10)

ESMOLOL

Esmolol is an ultra short acting second generation cardio-selective beta 1 receptor blocker. It has a rapid onset of action. It is devoid of any membrane stabilizing effects and has little intrinsic sympathomimetic activity. Esmolol is used mainly when a short duration of beta blockade is required or in patients who are critically ill. It is because in critically ill patients, side effects of beta blockers like hypotension, bradycardia or heart failure cannot be tolerated. Esmolol is administered only intravenously. The commercial preparation is buffered to a Ph of 4.5 – 5.5; this being one of the reasons for pain occurring on injection with esmolol. It is also classified as a class II anti arrhythmic drug.

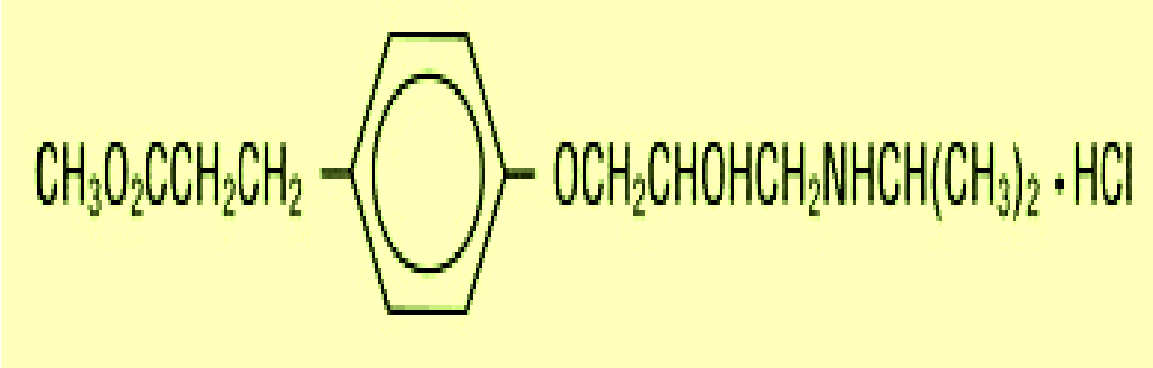


Fig.15: Structure of Esmolol hydrochloride.

ABSORPTION, FATE AND EXCRETION

Esmolol is administered slowly as an intravenous injection. It has a half life of approximately 8 minutes. The approximate volume of distribution is 2 liters' per kilogram. The most unique feature of the drug is its ester function that is incorporated into the phenoxy-propanolamine structure. This allows for rapid degradation of esmolol by plasma esterases. Less than 1 % is excreted unchanged in urine.(6) However the carboxylic acid metabolite of esmolol is longer acting with a half life of approximately 4 hours. Prolonged infusion of esmolol results in the accumulation of this metabolite, which finally gets excreted in urine. As the potency of this metabolite as a beta receptor antagonist is extremely low, it does not cause much adverse effects.

Less than 1% of the drug is excreted unchanged in urine and 75% of the drug is recovered as an inactive acid metabolite. Esmolol is compatible with most of the commonly used intravenous solutions and non depolarizing muscle relaxants. Esmolol

has poor lipid solubility, which limits its transfer across the placenta and blood brain barrier.

Esmolol has a negative inotropic and chronotropic effect. It decreases the conduction speed through the atrio-ventricular node and reduces the rate of spontaneous phase 4 de-polarization. The most common use of esmolol in surgical patients is either to prevent or treat tachycardia. Another common use is in the management of supraventricular tachycardia. Esmolol has a rapid onset of action, with peak concentration getting achieved in 3 to 10 minutes after giving the loading dose. There is considerable reduction of beta antagonism within 20 minutes of stopping the infusion. Normal patients exhibit striking hypotension with esmolol. The underlying mechanism for this hypotensive effect is not yet clear.

The drug esmolol is given in emergency settings where rapid beta blockade is required. So in the case of esmolol infusion, it is preceded by a loading dose. If the required effect is not seen within 5 minutes, the dose is repeated with the same loading dose but with a higher infusion rate of the maintenance dose. This can be continued until the desired effect is obtained. Esmolol is useful in situations where blood pressure, heart rate and cardiac output are elevated. It is also a useful drug to treat severe post operative hypertension. The American Heart Association does not recommend the use of esmolol in patients having bradycardia, patients who are on other beta blockers and in patients with decompensated heart failure as their myocardial function may be compromised. (10,31)

Dosage – In bolus dosing, esmolol at a dosage of 1.5 mg / kg over 30 seconds 3 minutes prior to laryngoscopy and endotracheal intubation effectively decreases the stress response.(1) In infusion dosing, continuous infusion of esmolol 50 to 300 µg/kg/minute following an initial bolus of 0.5 mg/kg over 30 seconds is also effective in decreasing the stress response. (6)

De Bruijn et al studied the haemodynamic effects of esmolol in chronically beta blocked patients undergoing aorto-coronary bypass surgery. They concluded that esmolol did not cause any further reduction of heart rate, in response to stress, in patients for whom chronic beta blocker therapy was continued till the time of surgery. The addition of esmolol however attenuated the increase in blood pressure when compared to the control group. (70)

In a study by Singh et al comparison was made between esmolol 1.4 mg/kg bolus with lignocaine 1.5 mg/kg and with nitroglycerine 2 microgram/kg. It was found that esmolol was more effective in reducing the the heart rate and mean arterial pressure response to intubation when compared to lignocaine. It was found that nitroglycerine, however could not effectively decrease the heart rate response to intubation.(71)

Sampangiramaiah Shailaja et al compared the effects of esmolol bolus 1.5mg/kg with esmolol bolus 1.5mg/kg together with fentanyl 2 microgram/kg in decreasing the stress response to laryngoscopy and intubation in patients with controlled hypertension. They found that esmolol 1.5mg/kg was effective in decreasing the cardiovascular stress

response to laryngoscopy and intubation without causing much haemodynamic disturbances whereas esmolol 1.5mg/kg together with fentanyl 2 microgram/kg was found to cause hypotension following intubation.(68)

Bakiye Ugur et al conducted a study comparing the effects of esmolol bolus 1.5mg/kg with lignocaine 1.5mg/kg and with fentanyl 1 microgram/kg on the haemodynamic stress response when given 2 minutes prior to intubation. It was observed that esmolol bolus was more effective in decreasing the intubation response. (72)

In another study conducted by Feng et al, esmolol 2 mg/kg was compared to fentanyl 3microgram/kg and lignocaine 2mg/kg. The study drug was given 3 minutes prior to intubation and they concluded that only esmolol bolus could offer reliable protection against tachycardia and rise in systolic blood pressure after laryngoscopy and intubation.(73)

Menigaux et al in his study has shown that esmolol prevents movement and attenuates BIS response to orotracheal intubation at a dose of 1mg/kg followed by 250 microgram / kg / minute. (74)

In a study by Wilson et al where esmolol 1mg / kg bolus was given followed by an infusion of 250 microgram / kg / minute, it was found that esmolol administered to un-stimulated anaesthetized patients has a peak effect at 1 to 2 minutes, although in some patients it can last up to 5 minutes. (75)

Like intubation, extubation also causes sympathetic stimulation which manifests as an increase in heart rate and blood pressure. Esmolol given at 0.5 mg/kg followed by 150

microgram/ kg /minute infusion effectively decreases the extubation response. (76)

There have been several studies done with Esmolol (either used alone as a bolus or as a small loading dose followed by infusion which has been aimed at noting the efficacy of this drug in reducing the stress response to laryngoscopy and intubation. One such study by Yazicioglu et al in which used a bolus dose of 1mg/kg esmolol 10 minutes before endotracheal intubation did not help suppress the haemodynamic stress response. So they suggested in their study that in cases where esmolol is given 10 minutes prior to intubation, an infusion would be better in reducing the stress response to endotracheal intubation. (77)

Miller DR et al in his study noticed that esmolol bolus when given along with a low dose narcotic effectively reduces the systolic blood pressure and heart rate response to intubation. (78)

P Gupta et al compared the effects of nitroglycerine infusion and esmolol infusion in decreasing the haemodynamic effects of intubation. They concluded that esmolol infusion effectively reduced the heart rate and blood pressure response to intubation more than nitroglycerine. (79)

Ersa Mercagnoolu Efe et al compared the effects of esmolol bolus with esmolol infusion on stress response during laryngoscopy, skin incision and sternotomy in coronary artery bypass graft surgery. In the bolus group they used a dosage of 1.5mg/kg and in the infusion group a dose of 500 microgram/kg/minute for 10 minutes before intubation which was continued for 5 minutes post intubation. They concluded that esmolol infusion

was more effective in controlling the systolic blood pressure change and the bolus was more effective in controlling the heart rate response to stress. (80)

Liu PL et al studied the effects of esmolol infusion in decreasing the stress response to intubation in 30 ASA I patients. The study group received an infusion of 500μg/kg/minute esmolol for 4 minutes followed by 300μg/kg/minute for 8 minutes thus adding up to a total duration of 12 minutes. Anaesthesia was induced five minutes after the start of esmolol infusion with thiopentone with succinyl choline being used for muscle relaxation. They concluded that even though esmolol infusion decreased the cardiovascular stress response to intubation, it did not eliminate it completely. (81)

EVOLVING DRUGS FOR ATTENUATING THE STRESS RESPONSE TO INTUBATION

Gabapentin

Originally used as an anticonvulsant, gabapentin has proved to be effective in controlling the stress response to intubation. Montazeri K et al conducted a study comparing the efficacy of oral clonidine 0.3mg with oral gabapentin 800mg premedication in decreasing the haemodynamic stress response to endotracheal intubation. The study drugs were given 90 minutes prior to surgery. Heart rate, systolic arterial pressure, diastolic arterial pressure , mean arterial pressure and rate pressure product were measured at baseline (3 min before induction), just before laryngoscopy, and post intubation (at 1, 3, 5, 10 and 15 min after starting laryngoscopy).This study demonstrated that premedication with oral

gabapentin 800 mg or clonidine 0.3 mg had a similar blunting of the hyperdynamic response after laryngoscopy and intubation.(82)

Memis et al compared two doses of oral gabepentin 400mg and 800mg and their efficacy in reduction of stress response to intubation. The study drug was given one hour prior to surgery. Changes in heart rate and mean arterial pressure were monitored after intubation. They concluded that oral gabapentin 800mg given one hour prior to surgery was a safe and effective method to decrease the stress response to intubation.(83)

Nalbuphine

Nalbuphine is a synthetic opioid agonist-antagonist. It acts as an agonist at the κ receptor and as an antagonist at the μ receptor. It has been tested for decreasing the haemodynamic stress response to intubation. Kothari et al compared the efficacy of pentazocine with nalbuphine to decrease the stress response to intubation in ASAI and II patients. Nalbuphine 0.2mg/kg or pentazocine 0.5mg/kg was given 5 minutes before induction of anaesthesia. Thiopentone was the induction agent used and intubation was performed after administration of succinyl choline. They concluded in their study that nalbuphine effectively reduces hypertension, tachycardia and cardiac workload associated with endotracheal intubation.(84)

Landiolol

Landiolol is a newly developed short acting beta 1 receptor blocker. It has been tried for the attenuation of cardiovascular responses to intubation. Goyagi et al used landiolol

125µg/kg/min for one minute followed by 40µg/kg/min infusion for four minutes in their study. Anesthesia was induced four minutes after starting landiolol, with propofol and succinyl choline. They noticed a fall in heart rate and systolic blood pressure in the pre-intubation period after the administration of landiolol. They concluded in their study that continuous administration of landiolol helps in decreasing the stress response to intubation.(85)

Pregabalin

Pregabalin is a calcium channel blocker which decreases the release of glutamine, substance P and nor adrenaline. Gupta et al gave oral pregabalin 150mg as premedication 60-75 minutes before surgery. They noticed that pregabalin significantly decreased the hypertensive response to intubation, but the heart rate response to intubation was not effectively reduced.(86)

Lornoxicam

Lornoxicam is a non steroidal anti-inflammatory drug. Daarbiss et al studied the efficacy of lornoxicam in decreasing the stress response to intubation. In their study they concluded that 16mg of lornoxicam given 30 minutes before surgery effectively reduced the pressor response to intubation.(87)

MATERIALS AND METHODS

- Study design
- Study population
- Sample size calculation
- Anaesthesia protocol
- Premedication
- Pre-induction period
- Induction and maintenance
- Protocol
- Results
- Statistical analysis

METHODS

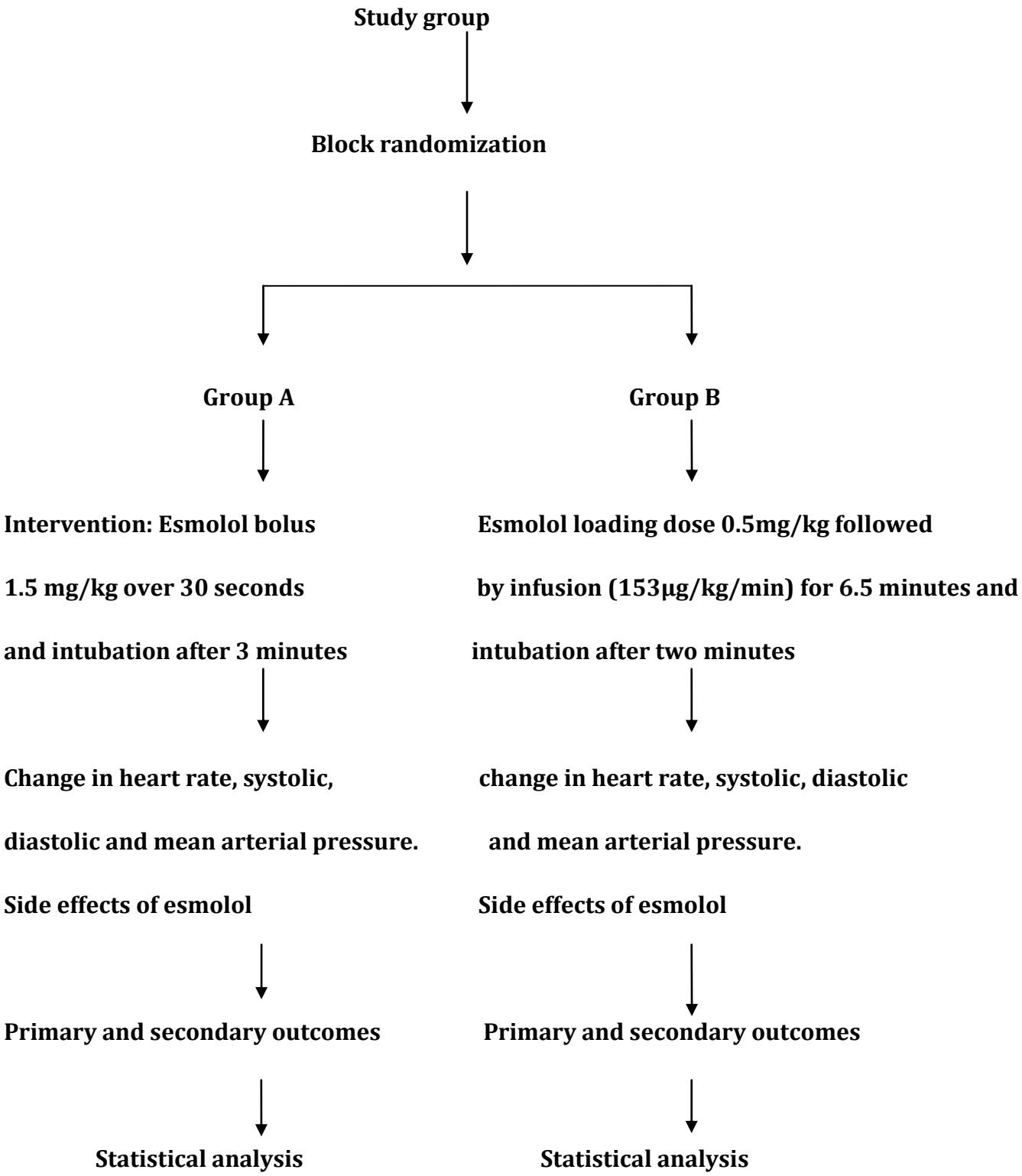
STUDY DESIGN

After obtaining the approval of the Institutional Review Board, we conducted a randomized controlled trial comparing Esmolol bolus with Esmolol infusion in reducing the peri-intubation stress response in non cardiac surgical patients undergoing general anaesthesia with endotracheal intubation.

Various drugs have been used to decrease the stress response to intubation. Esmolol is an ultra short acting beta 1 blocker which has been proven to be beneficial and more effective than many of the commonly used drugs in reducing the intubation response.

Esmolol itself can either be used as an infusion or as a bolus for the purpose of decreasing the intubation response. The aim of our study is to find out which mode of administration of esmolol reduces intubation response effectively with minimal side effects.

FLOW CHART


Study group
Block randomization
Group A
Group B
Intervention: Esmolol bolus
1.5 mg/kg over 30 seconds
and intubation after 3 minutes
Esmolol loading dose 0.5mg/kg followed
by infusion (153µg/kg/min) for 6.5 minutes and
intubation after two minutes
Change in heart rate, systolic,
diastolic and mean arterial pressure.
Side effects of esmolol
change in heart rate, systolic, diastolic
and mean arterial pressure.
Side effects of esmolol
Primary and secondary outcomes
Primary and secondary outcomes
Statistical analysis
Statistical analysis

STUDY POPULATION

Inclusion Criteria:

-Adult patients in the age group of 18-70 years admitted for non cardiac surgery and have consented for the study

Exclusion Criteria:

-Pregnancy

-Heart rate less than 60 per minute

-Systolic blood pressure less than 100mm Hg

-Hepatic failure

-Renal failure

-Cardiac conduction abnormalities

-Patients on beta blockers

-History of asthma or chronic obstructive pulmonary disease

-History of intolerance to beta blockers

-Obesity (body mass index more than 30)

-Total duration of laryngoscopy more than 30 seconds

-Patients who are unable to understand and give consent for participation.

-Patients less than 18 and more than 70 years old.

-Patients who are part of other studies.

-Difficult airway. (appendix 1)

- ASA PS III and IV. (appendix 2)

SAMPLE SIZE CALCULATION

Sample size for comparing two proportions

P1 –P2 = d

P1 = effective beta blockade with minimal side effects in esmolol infusion group

P2 = = effective beta blockade with minimal side effects in esmolol bolus group.

P1 =90% P2 = 70%

P1 –P2 =d

ie 90 – 70 = 20

$\bar{P} = (P1 + P2) / 2 = (90 + 70) / 2 = 80$

$d / SE = Z\alpha$

$d / \sqrt{(PQ/n1 + PQ/n2)} = Z\alpha$

$d / \sqrt{2}(PQ/n) = Z\alpha$

$n = ([2*PQ] / d^2) * Z\alpha^2$

$n = ([2*PQ] / d^2) * (Z\alpha + Z\beta)^2$

$n = (2 * 80*20* (1.96+ 0.84)^2) / 20 *20$

= 63 in each arm

SE = standard error

n 1 = number in P1 group

n 2 = number in P2 group

Zα = type 1 error = 0.05 = 1.96

Zβ = type 2 error = 0.2 = 0.84

Methodology

An informed consent was obtained from the participants of the study as an initial step. The patients were given an oral pre-medication consisting of tablet diazepam 5mg and tablet metaclopramide 10mg at approximately 2 hours prior to surgery. Vasoactive drugs like atropine, ephedrine and phenylephrine along with all other emergency drugs were kept ready inside the theatre. After shifting the patient to the operating table, the first step was to obtain a peripheral intravenous access. Then monitors like pulse oximeter, 5 lead ECG and non invasive blood pressure monitoring were attached and baseline oxygen saturation, heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure were recorded.

The induction of anaesthesia was similar for both groups in which fentanyl 2mcg/kg, propofol 2mg/kg, isoflurane 2% and atracurium 0.5mg/kg was used. Minimum alveolar concentration of Isoflurane at the time of intubation was kept between 0.8-0.9 for all patients.

In the esmolol bolus group, a pre calculated dose of esmolol (1.5mg/kg) was given over 30 seconds following administration of the muscle relaxant. The patient was then intubated after a period of 3 minutes.

In the esmolol infusion group, a loading dose of esmolol 0.5 mg /kg was given over 30 seconds through a dedicated intravenous line, followed by an infusion of 150mcg/kg/min over 6.5 minutes, thereby making it a total of 7 minutes. The patient was induced 5

minutes after starting the infusion and endotracheal intubation performed 2 minutes after stopping the infusion.

In both groups' heart rate, systolic, diastolic and mean blood pressures were monitored; immediately after attaching the monitors (baseline), every minute prior to intubation for 2 minutes, and every minute post intubation for 5 minutes. Intubation was performed by an anaesthesiologist who had completed a minimum of one year training in our department. The intubation time calculated from the time of removal of the face mask to the inflation of the endotracheal tube cuff was kept to less than 30 seconds. The intubation time was monitored by an assistant on the clock. Anaesthesia was maintained with oxygen, air, isoflurane and top ups of muscle relaxant.

Any significant change, which was taken as a change of ±20 % from the baseline, is recorded. A reduction in heart rate to less than 60 per minute or a fall in mean arterial pressure to less than 60 mmHg or a 20 % change from the baseline value which was not getting corrected within the next 2 minutes warranted an intervention. It was decided to wait for 2 minutes before intervening as esmolol is an ultra short acting beta blocker whereby the changes in blood pressure and heart rate caused by the drug stabilises rapidly.

A decrease in heart rate was treated with injection atropine (0.3- 0.6mg) and a fall in blood pressure was treated with injection ephedrine (5-10mg) or injection phenylephrine(50-100µg). An increase in heart rate and blood pressure was treated with small bolus doses (0.25-0.5mg/kg) of injection propofol or injection fentanyl (10-20mcgs).

Calculation of dose for infusion: In order to maintain uniformity, the total dose of drug given in both groups was kept at 1.5mg/kg. First the total dose of drug was calculated at 1.5mg/kg body weight of which 0.5 mg/kg was given as bolus over 30 seconds. Remaining 1mg/kg was given as infusion over 6.5 minutes so that the total duration of drug administration in the infusion group was 7 minutes.

The infusion rate was calculated in the following manner:

1 mg/kg of esmolol was taken in a 20 cc syringe and diluted to make each ml 5 mg/kg.

Patient weight / 6.5 gave the dose that needed to be given in mg per minute

Since each ml was 5 mg, dose to be given in mg per minute divided by 5 gave the dose in ml per minute.That value multiplied by 60 gave the rate to be infused in ml per hour.

The arterial extension was flushed separately with esmolol 5mg/ml to remove the dead space and then attached to a 20cc syringe to start the infusion.

By using the above mentioned calculation, the approximate infusion dose that the patient received was 153 microgram / kg / minute after the initial bolus of 0.5 mg/kg.

RESULTS AND ANALYSIS

BASELINE VALUES

VARIABLE	INFUSION (N=44)	BOLUS (N=45)	P VALUE
MALE/FEMALE	28/16	30/5	0.76[a]
AGE mean (sd)	36.39(11.65)	34.42(12.27)	0.441[b]
BMI mean(sd)	24(3.17)	22.7(3.52)	0.072[b]
BASELINE HR mean(sd)	83.59(14.85)	84.4(13.51)	0.788[b]
BASELINE SBP mean (sd)	133.55(19.41)	129.49(18.78)	0.319[b]
BASELINE DBP mean (sd)	82.64(12.87)	77.56(10.73)	0.046[b]
BASELINE MAP mean (sd)	99.59(14.53)	94.96(12.69)	0.112[b]

Table.1: Comparison of demographic and baseline variables in Esmolol bolus and infusion groups.

[a]=chi square, [b]= t test

sd= standard deviation.

BMI = Body mass index

HR = Heart rate

SBP = Systolic blood pressure

DBP = Diastolic blood pressure

MAP = Mean arterial pressure

All the baseline variables between the two groups were comparable as the p value is more than 0.05. In diastolic blood pressure p value was 0.046 which is approximately equal to p=0.05.

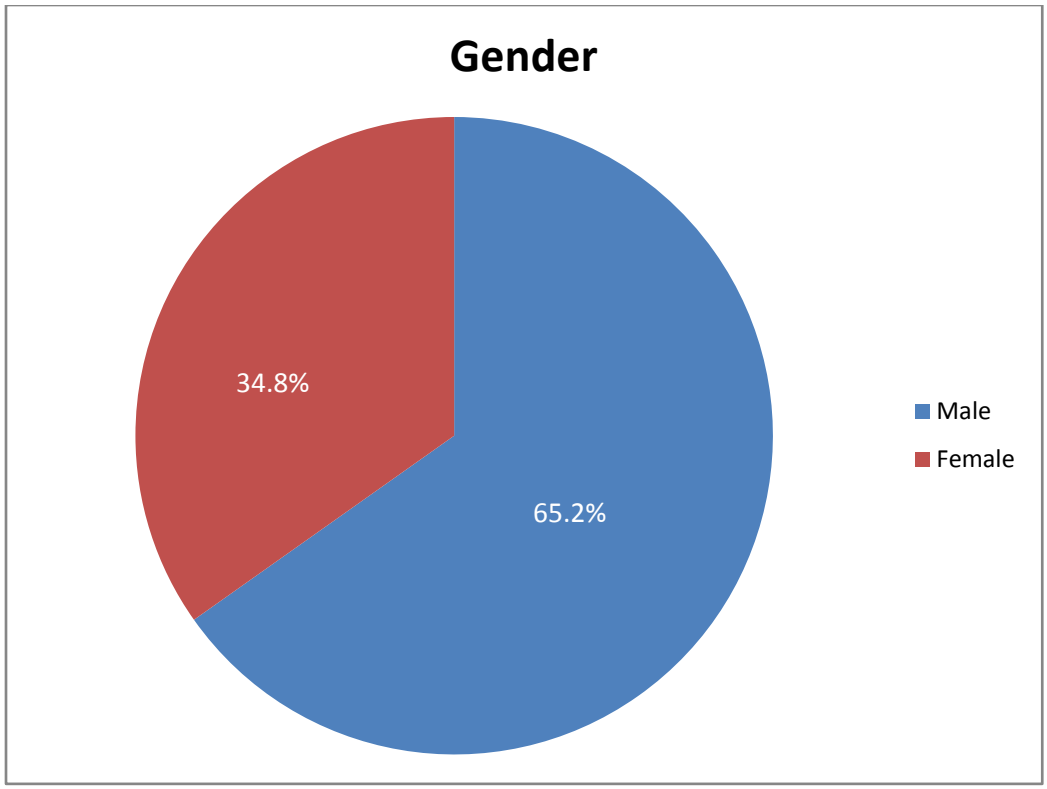


Fig.16: Pie diagram showing the gender distribution.

The pie diagram shows the percentage of males and females who participated in the study. The study had a total number of 58 males and 31 females which corresponded to 65.2% and 34.8% respectively. While the infusion group had 28 males, the bolus group had 30 males. The number of females was 16 and 15 in the infusion and bolus group respectively. The p value of 0.76 obtained for gender distribution between the bolus and infusion group states that there is no statistically significant difference in the number of males and females in both the groups.

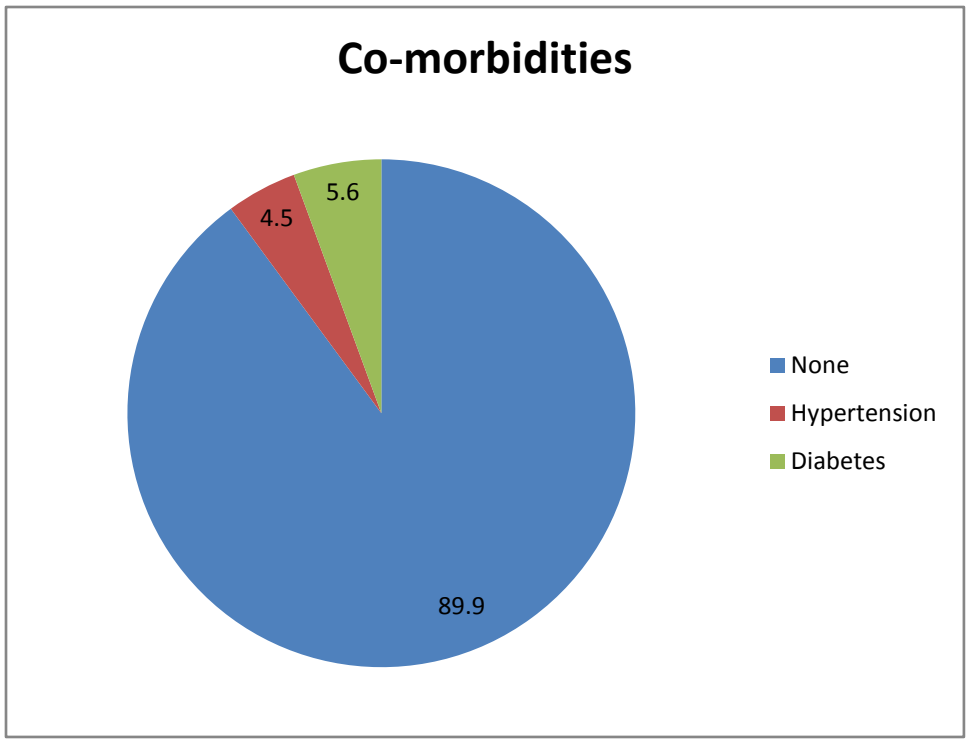


Fig.17: Pie diagram showing the distribution of co-morbidities in the study population.

Though the study included all non cardiac surgical patients, the majority of the participants were ASA 1 patients. The infusion group had 38 patients without any co-morbidity whereas the bolus group had 42 patients of the same. 6 patients in the infusion group had some associated co-morbidity. Of the 6, two were hypertensives and four were diabetics. The bolus group had 3 patients with associated co-morbidities. Of the 3, two were hypertensives and one, a diabetic. This has been summarized in the pie- chart above.

Overall, while hypertensives constituted 4.5% of the study population, 5.6% were diabetics. There was no statistically significant difference in co-morbidities between the two groups as the p value obtained was 0.276.

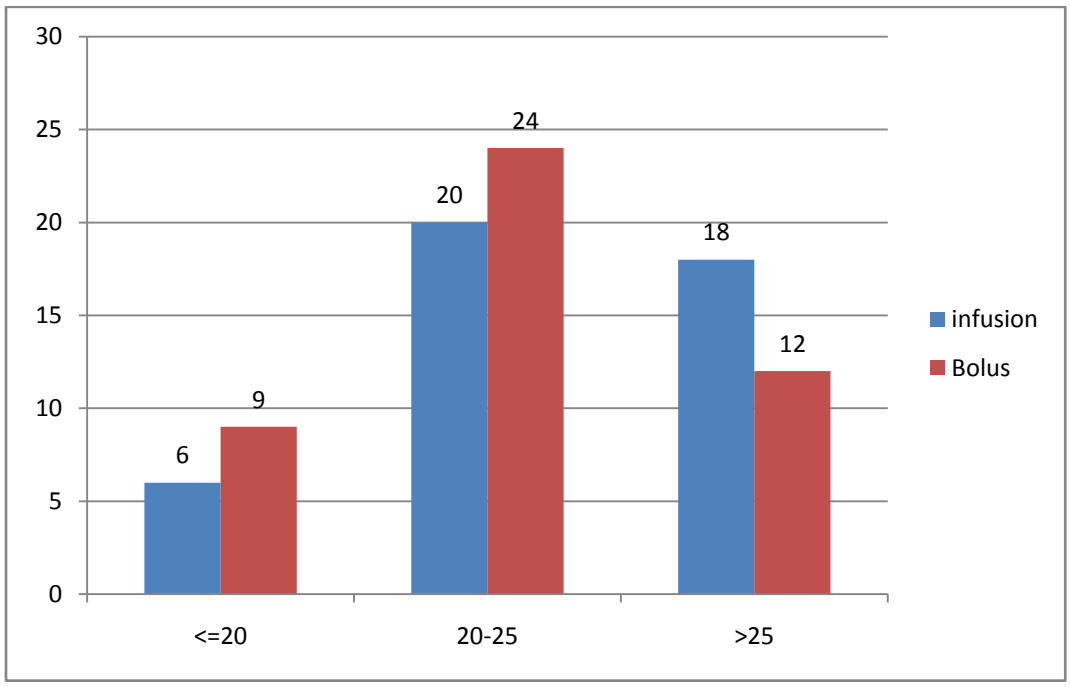


Fig.18: Comparison of the body mass index of the study population in Esmolol bolus group with Esmolol infusion group.

BMI (kg/m^2)	Infusion	Bolus
≤20	6	9
20-25	20	24
≥25	18	12

This graph shows body mass index along the X axis and number of patients along the Y axis. Maximum number of patients in the infusion and bolus group was in the body mass index range of 20 to 25 kg/m^2. There was no statistically significant difference between the two groups with regards to body mass index as the p value was 0.072.

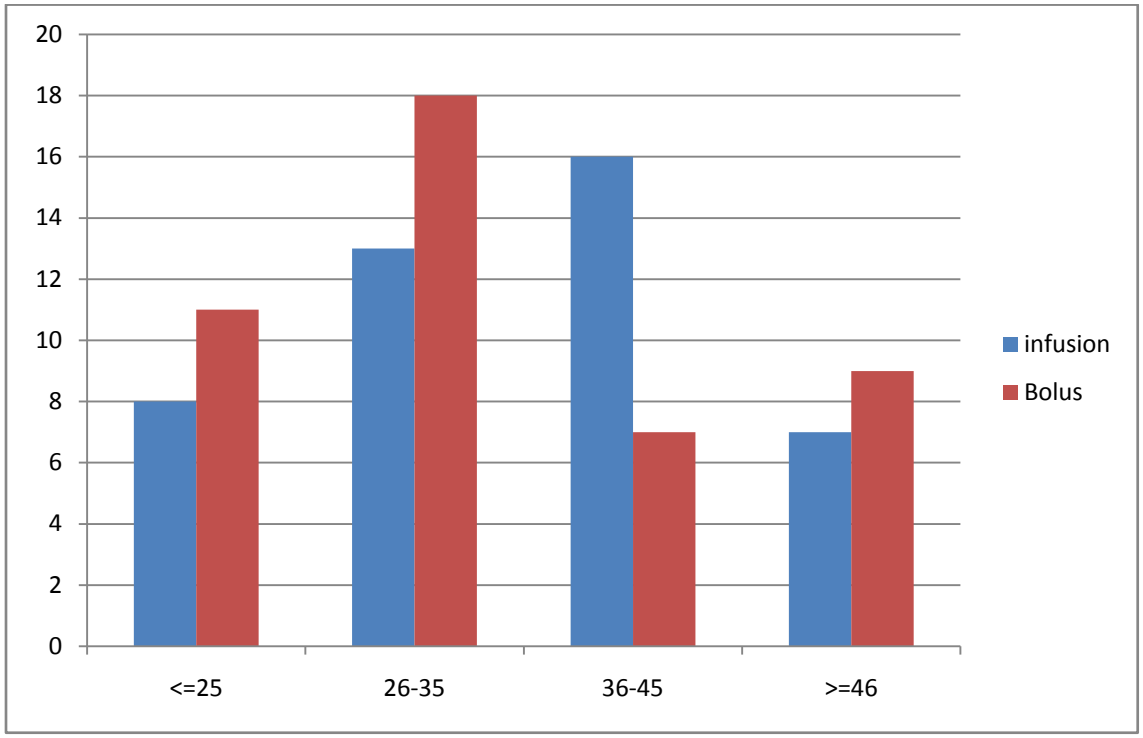


Fig.19: Comparison of the age of the study population in Esmolol bolus group with Esmolol infusion group.

Age group	Infusion	Bolus
≤25	8	11
26-35	13	18
36-45	16	7
≥45	7	9

In the above graph, age is shown along the X axis and number of patients along the y axis. There was no statistically significant age difference between the two groups as the p value was more than 0.05.

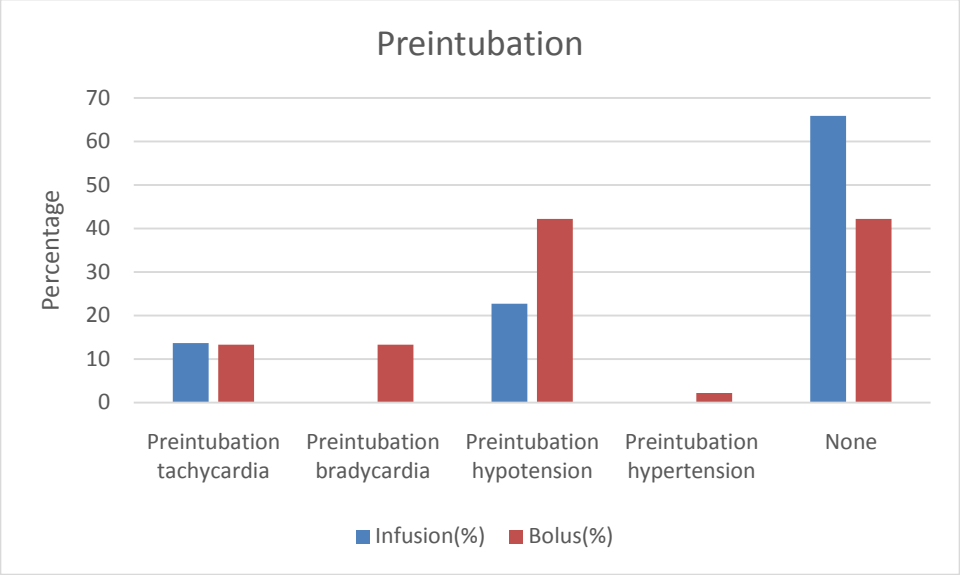


Fig.20: comparison of pre-intubation haemodynamic changes between Esmolol bolus with Esmolol infusion group.

Pre-intubation	Infusion: n (%)	Bolus: n (%)	P value
tachycardia	6 (13.64)	6 (13.33)	0.96[b]
bradycardia	0 (0)	6 (13.33)	0.012[b]
hypotension	10 (22.73)	19 (42.22)	0.05[b]
hypertension	0 (0)	1 (2.22)	0.320[b]
none	29 (56.82)	19 (15.56)	0.025[b]

Table.2: Comparison of pre-intubation haemodynamic variables between Esmolol bolus and infusion groups.

[b]= t test; n = number

6 patients in the bolus group and 6 of the infusion group had pre-intubation tachycardia. Pre-intubation hypotension was present in 10 and 19 patients respectively of the infusion and bolus group respectively. While none of the patients in the infusion group had pre-intubation hypertension, one patient in the bolus group had pre-intubation hypertension. No other complications were noted in the study group during this period. As the p value

for tachycardia, hypotension and hypertension is not less than 0.05, there was no statistically significant difference between the two groups.

While 6 patients in the bolus group had pre-intubation bradycardia, none of the participants in the infusion group had pre-intubation bradycardia. The p value for bradycardia between the two groups was 0.012 which is statistically significant. Haemodynamic instability was absent in 29 patients of the infusion group whereas the corresponding figure for those in the bolus group was 19. The p value between the two groups was 0.025 and it was found to be statistically significant.

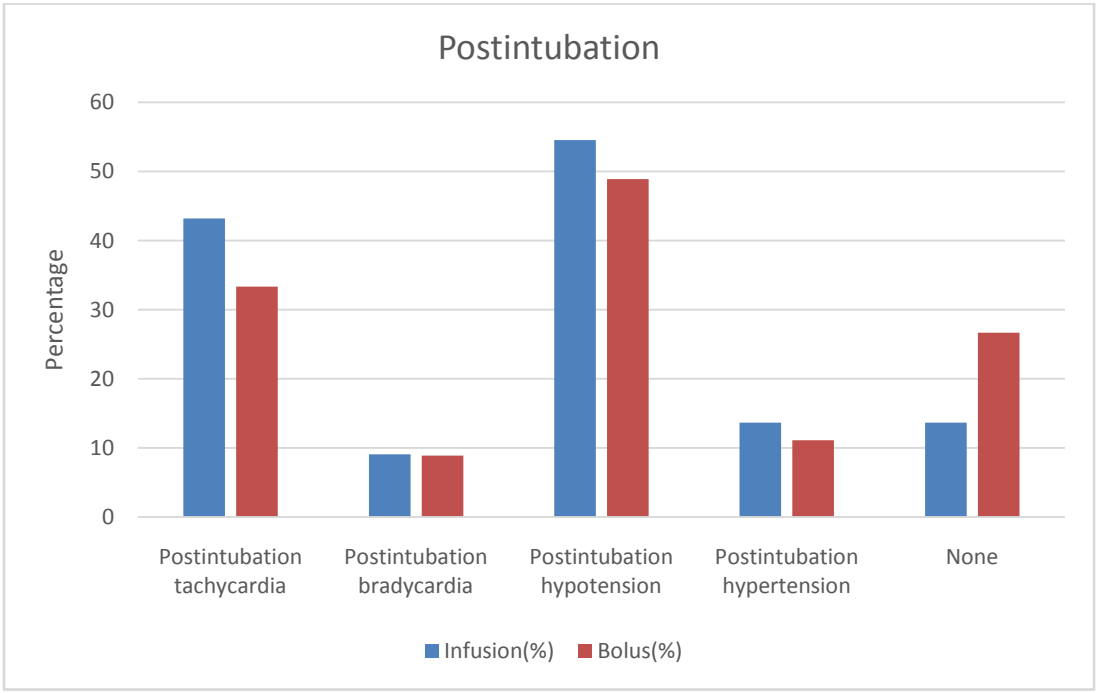


Fig.21: Comparison of post-intubation haemodynamic changes between Esmolol bolus and Esmolol infusion group.

Post intubation	Infusion n (%)	Bolus n (%)	P value
tachycardia	19 (43.18)	15 (33.33)	0.339[b]
bradycardia	4 (9.09)	4 (8.89)	0.973[b]
hypotension	24 (54.55)	22 (48.89)	0.593[b]
hypertension	6 (13.64)	5 (11.11)	0.717[b]
none	6 (13.64)	12 (26.67)	0.126[b]

Table.3: Comparison of post-intubation haemodynamic variables between Esmolol bolus and Esmolol infusion groups.

[b]= t test, n = number

Following intubation, among the infusion group, 19 patients had tachycardia, 4 had bradycardia, 24 had hypotension and 6 patients had hypertension. Correspondingly among the bolus group, 15 patients had tachycardia, 4 had bradycardia, 22 had hypotension and 5 patients had hypertension. As the p value between the variables of the two groups were more than 0.05, the differences were statistically insignificant.

While 6 patients of the infusion group did not show any post intubation haemodynamic instability, the corresponding number for those the bolus group was 12. The p value obtained was 0.126; thereby proving the difference between the two groups to be statistically insignificant.

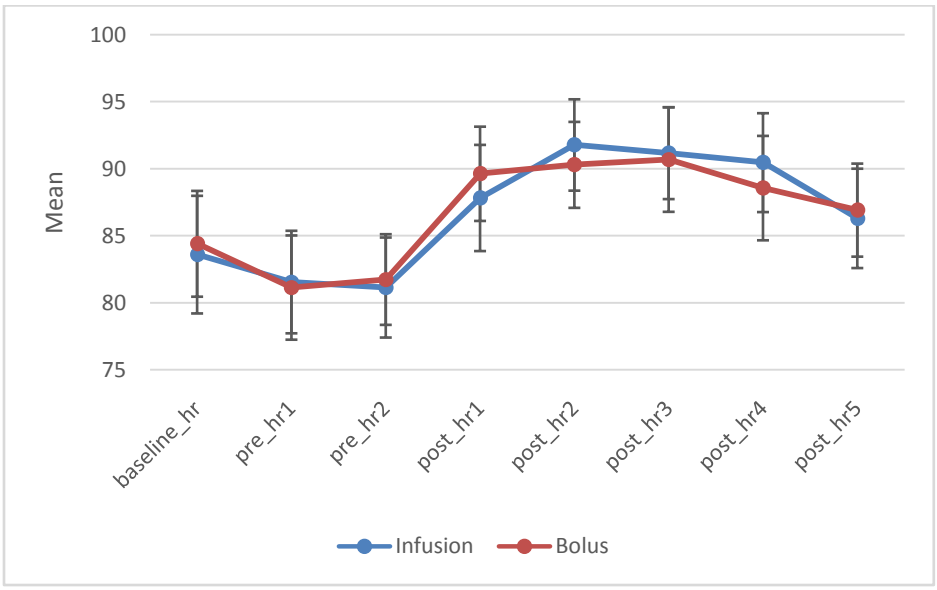


Fig.22: Comparison of Esmolol bolus and Esmolol infusion with regards to changes in heart rate over a period of 2 minutes pre-intubation to 5 minutes post-intubation.

	INFUSION MEAN (95%CI)	BOLUS MEAN (95%CI)
Baseline heart rate	83.59 (79.2,87.98)	84.4 (80.45,88.35)
Pre-intubation heart rate 1	81.55 (77.72,85.37)	81.13 (77.24,85.02)
Pre-intubation heart rate 2	81.14 (77.4,84.87)	81.73 (78.35,85.11)
Post-intubation heart rate 1	87.82 (83.86,91.78)	89.62 (86.11,93.14)
Post-intubation heart rate 2	91.77 (88.36,95.18)	90.29 (87.08,93.5)
Post-intubation heart rate 3	91.16 (87.74,94.58)	90.69 (86.79,94.59)
Post-intubation heart rate 4	90.45 (86.77,94.14)	88.56 (84.66,92.45)
Post-intubation heart rate 5	86.3 (82.59,90)	86.91 (83.44,90.38)

Table.4: Table comparing mean values of heart rates in Esmolol infusion and bolus groups.

CI = confidence interval

As the time changes there is a significant difference in heart rate ($p < 0.001$), but the difference between two arms is not clinically significant. ($p=0.86$).

Time	P value
Pre-intubation 1st minute	0.268
Pre-intubation 2nd minute	0.184
Post-intubation 1st minute	0.022
Post-intubation 2nd minute	<0.001
Post-intubation 3rd minute	<0.001
Post-intubation 4th minute	<0.001
Post-intubation 5th minute	0.143

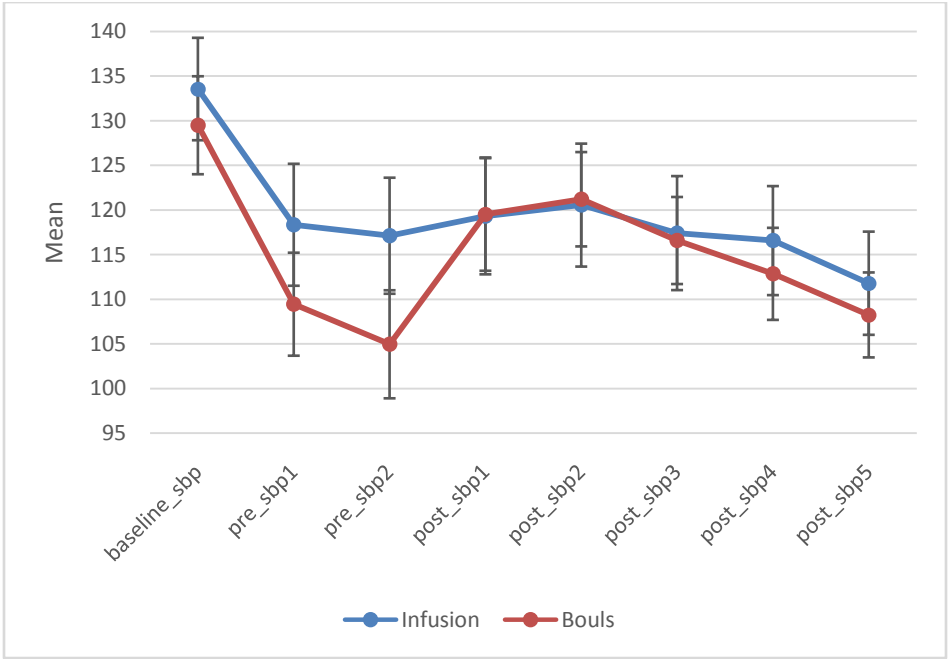
Table.5: Statistical significance of the changes in heart rate from the base line value per unit time in the esmolol infusion group.

In the infusion group, there is a fall in heart rate in the pre-intubation period as evidenced from the graph. But the fall from the baseline value is not statistically significant as the p value for the difference in heart rate between the baseline and the first and second minute pre-intubation is more than 0.05.Immediately after intubation there is a rise in heart rate from the baseline which stabilizes in the fifth minute. The post-intubation rise in heart rate from the baseline for the first four minutes is statistically significant as the p value is less than 0.05. Thus, we infer that esmolol infusion failed to protect effectively against post-intubation tachycardia in this study.

Time	P value
Pre-intubation 1st minute	0.074
Pre-intubation 2nd minute	0.144
Post-intubation 1st minute	0.004
Post-intubation 2nd minute	0.001
Post-intubation 3rd minute	0.001
Post-intubation 4th minute	0.023
Post-intubation 5th minute	0.169

Table.6: Statistical significance of changes in heart rate from the base line value per unit time in the esmolol bolus group.

In the bolus group, there is a decrease in heart rate in the pre-intubation period with the bolus dose of esmolol. But the fall in heart rate from the baseline value was not statistically significant as the p value for the first and second pre-intubation minutes were more than 0.05. Immediately after intubation there is a rise in heart rate from the baseline which is getting stabilized in the fifth minute. The post-intubation rise in heart rate for the first four minutes was statistically significant as the p value was less than 0.05. Thus, bolus dose of esmolol also failed to effectively protect against post-intubation tachycardia.



sbp = systolic blood pressure

pre = pre-intubation

post = post-intubation

1- first minute

2- second minute

3- third minute

4- fourth minute

5- fifth minute

Fig.23: Comparison of Esmolol bolus and infusion with regards to changes in systolic blood pressure over a period of 2 minutes pre-intubation to 5 minutes post-intubation.

	INFUSION MEAN (95% CI)	BOLUS MEAN (95% CI)
Baseline SBP	133.55(127.81,139.28)	129.49(124,134.98)
Pre-intubation SBP 1	118.34(111.51,125.17)	109.44(103.68,115.21)
Pre-intubation SBP 2	117.11(110.62,123.61)	104.96(98.91,111.01)
Post-intubation SBP 1	119.3(112.79,125.8)	119.53(113.19,125.88)
Post-intubation SBP 2	120.55(113.66,127.43)	121.2(115.92,126.48)
Post-intubation SBP 3	117.41(111.03,123.79)	116.58(111.7,121.45)
Post-intubation SBP 4	116.57(110.46,122.67)	112.84(107.69,118)
Post-intubation SBP 5	111.8(106.02,117.57)	108.24(103.49,113)

Table.7: Table comparing mean values of systolic blood pressure in Esmolol infusion and bolus groups.

CI = confidence interval, SBP = systolic blood pressure

As the time changes there is a significant difference in systolic blood pressure ($p<0.001$). The difference between the two arms is also showing significance as the p value is less than 0.05 ($p= 0.0383$). But this difference could be due to the pre-intubation differences in the systolic blood pressure between the two arms. The difference is getting stabilized in the post-intubation period.

Time	P value
Pre-intubation 1st minute	<0.001
Pre-intubation 2nd minute	<0.001
Post-intubation 1st minute	<0.001
Post-intubation 2nd minute	<0.001
Post-intubation 3rd minute	<0.001
Post-intubation 4th minute	<0.001
Post-intubation 5th minute	<0.001

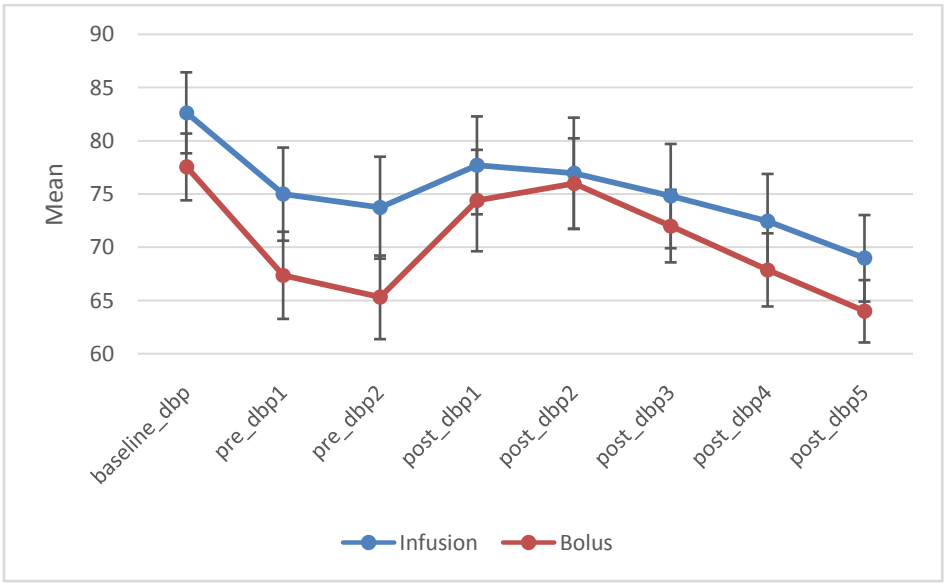
Table.8: Statistical significance of the changes in systolic blood pressure from the base line value per unit time in the esmolol infusion group.

There is statistically significant decrease in the systolic blood pressure in the pre-intubation and post-intubation period in the esmolol infusion group (p value < 0.05).

Time	P value
Pre-intubation 1st minute	<0.001
Pre-intubation 2nd minute	<0.001
Post-intubation 1st minute	0.001
Post-intubation 2nd minute	0.007
Post-intubation 3rd minute	<0.001
Post-intubation 4th minute	<0.001
Post-intubation 5th minute	<0.001

Table.9: Statistical significance of the changes in systolic blood pressure from the base line value per unit time in the esmolol bolus group.

There is a statistically significant fall in systolic blood pressure in the pre-intubation and post-intubation period when compared to the baseline (p value < 0.05).



dbp = diastolic blood pressure

pre = pre-intubation

post = post-intubation

1- first minute

2- second minute

3- third minute

4- fourth minute

5- fifth minute

Fig.24: Comparison of Esmolol bolus and infusion with regards to changes in diastolic blood pressure over a period of 2 minutes pre-intubation to 5 minutes post-intubation.

	INFUSION MEAN(95% CI)	BOLUS MEAN (95%CI)
Baseline DBP	82.64(78.83,86.44)	77.56(74.42,80.69)
Pre-intubation DBP 1	75(70.63,79.37)	67.38(63.28,71.47)
Pre-intubation DBP 2	73.73(68.94,78.51)	65.31(61.39,69.24)
Post-intubation DBP 1	77.7(73.11,82.3)	74.4(69.64,79.16)
Post-intubation DBP 2	76.95(71.72,82.18)	76(71.76,80.24)
Post-intubation DBP 3	74.82(69.92,79.72)	72(68.59,75.41)
Post-intubation DBP 4	72.43(67.96,76.9)	67.89(64.46,71.32)
Post-intubation DBP 5	68.98(64.92,73.04)	64(61.07,66.93)

Table.10: Table comparing mean values of diastolic blood pressure in Esmolol infusion and bolus groups.

CI = confidence interval; DBP = Diastolic blood pressure

There is a significant difference in the change of diastolic blood pressure within the two arms from the baseline to the 5^{th} minute post intubation (p=0.0001). But there is no statistically significant difference between the two arms (p = 0.3676).

Time	P value
Pre-intubation 1^{st} minute	0.001
Pre-intubation 2^{nd} minute	<0.001
Post-intubation 1^{st} minute	0.037
Post-intubation 2^{nd} minute	0.016
Post-intubation 3^{rd} minute	0.001
Post-intubation 4^{th}	<0.001
Post-intubation 5^{th}	<0.001

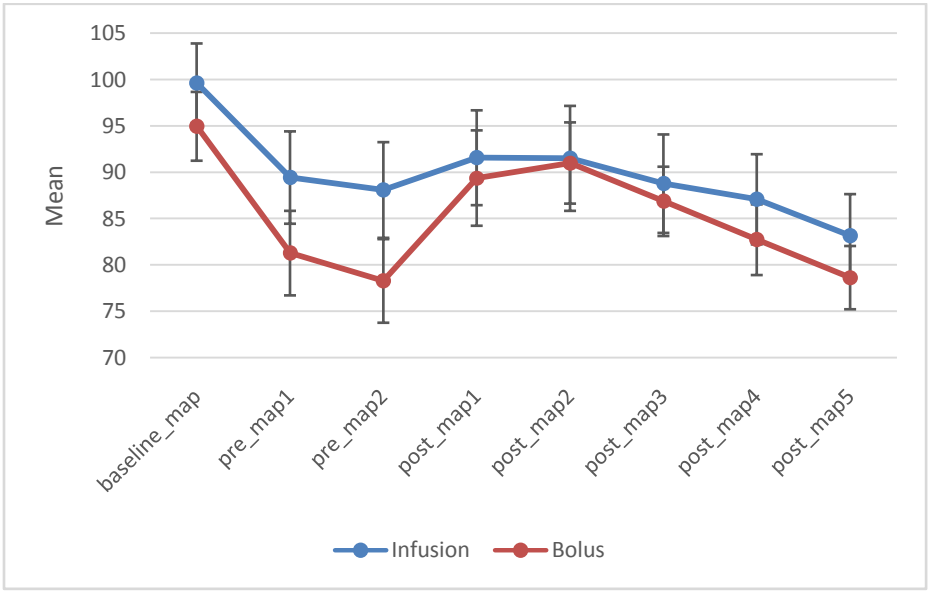
Table.11: Statistical significance of the changes in diastolic blood pressure from the base line value per unit time in the esmolol infusion group.

Diastolic blood pressure showed a significant fall in the pre-intubation and post-intubation period in the esmolol infusion group.

Time	P value
Pre-intubation 1st minute	<0.001
Pre-intubation 2nd minute	<0.001
Post-intubation 1st minute	0.177
Post-intubation 2nd minute	0.506
Post-intubation 3rd minute	0.018
Post-intubation 4thminute	<0.000
Post-intubation 5thminute	<0.000

Table.12: Statistical significance of the changes in diastolic blood pressure from the base line value per unit time in the esmolol bolus group.

In the bolus group, there is a significant fall in the diastolic blood pressure in the pre-intubation period from the baseline (p value< 0.05). The changes when compared to the baseline value in the first 3 minutes post-intubation are not statistically significant. After the third post-intubation minute, the diastolic blood pressure again falls significantly (p value< 0.05).



map = mean arterial blood pressure

pre = pre-intubation

post = post-intubation

1- first minute

2- second minute

3- third minute

4- fourth minute

5- fifth minute

Fig.25: Comparison of Esmolol bolus and infusion with regards to change in mean arterial pressure over a period of 2 minutes pre-intubation to 5 minutes post-intubation.

	INFUSION MEAN (95% CI)	BOLUS (95% CI)
Baseline MAP	99.59(95.3,103.88)	94.96(91.25,98.66)
Pre-intubation MAP 1	89.43(84.46,94.41)	81.29(76.73,85.84)
Pre-intubation MAP 2	88.09(82.93,93.25)	78.29(73.78,82.79)
Post-intubation MAP 1	91.57(86.46,96.68)	89.38(84.24,94.52)
Post-intubation MAP 2	91.5(85.84,97.16)	91(86.62,95.38)
Post-intubation MAP 3	88.77(83.47,94.08)	86.87(83.13,90.6)
Post-intubation MAP 4	87.09(82.23,91.95)	82.73(78.92,86.54)
Post-intubation MAP 5	83.16(78.67,87.65)	78.64(75.23,82.06)

Table.13: Table comparing mean values of mean arterial pressure in Esmolol infusion and bolus groups.

CI = confidence interval; MAP = mean arterial blood pressure

As the time change there is a significant decrease in the mean arterial pressure within the two arms ($p < 0.001$). However, the change in mean arterial pressure does not show any statistically significant difference between the two arm ($p=0.1334$)

Time	P value
Pre-intubation 1st minute	<0.001
Pre-intubation 2nd minute	<0.001
Post-intubation 1st minute	0.001
Post-intubation 2nd minute	0.001
Post-intubation 3rd minute	<0.001
Post-intubation 4th minute	<0.001
Post-intubation 5th minute	<0.001

Table.14: Statistical significance of the changes in mean arterial blood pressure from the base line value per unit time in the esmolol infusion group.

In the infusion group there is a significant fall in mean arterial pressure in the pre-intubation period from the baseline (p value< 0.05). It stabilizes in the initial two minutes post intubation, but after that there is a significant fall in mean arterial pressure (p value< 0.05)

Time	P value
Pre-intubation 1st minute	<0.001
Pre-intubation 2nd minute	<0.001
Post-intubation 1st minute	0.025
Post-intubation 2nd minute	0.111
Post-intubation 3rd minute	0.001
Post-intubation 4th minute	<0.001
Post-intubation 5th minute	<0.001

Table.15: Statistical significance of the changes in mean arterial blood pressure from the base line value per unit time in the esmolol bolus group.

In the bolus group, there is a significant fall in mean arterial pressure in the pre-intubation period from the baseline (p value< 0.05). It stabilizes in the initial two minutes after intubation, but after that there is a significant fall in mean arterial pressure (p value< 0.05)

STATISTICAL METHODS

The data was summarized using mean along with standard deviation for continuous variables, and frequency along with percentage for categorical variables. Repeated measure ANOVA was used to compare the time change between the two intervention arms. Independent t- test and Chi-square test was used to analyze the baseline difference among the intervention arms depending on the variable nature (continuous/categorical). The significance for all tests was performed at 5% levels. All statistical analysis were performed using STATA I/C 13.1 software. A p value of less than 0.05 was taken as significant.

DISCUSSION

This randomized controlled study was designed to find out the haemodynamic effects of the different modes of administration of esmolol on stress response to laryngoscopy and endotracheal intubation. As there are very few studies comparing the effects of esmolol bolus with esmolol infusion, we decided to compare the two different modes of esmolol administration and its effect on decreasing the stress response to laryngoscopy and intubation.

In our study, with regards to changes in systolic pressure, it was found that there existed a significant difference between the two groups. This difference was due to the fact that the pre-intubation fall in systolic blood pressure was more with the esmolol bolus group when compared to the infusion group. But these changes were seen to stabilize in the post intubation period. It was concluded in the study by Ersa Mercagnoolu Efe et al that there is no significant difference between esmolol bolus and infusion in decreasing the stress response.(80) The same result was obtained in our study except for the pre-intubation difference in systolic blood pressure.

Shailaja S et al compared the effects of esmolol bolus 1.5mg/kg with esmolol bolus 1.5mg/kg along with fentanyl 2 microgram/kg in decreasing the stress response to laryngoscopy and intubation in patients with controlled hypertension. They found that esmolol 1.5mg/kg was effective in decreasing the stress response to laryngoscopy and intubation without causing much haemodynamic disturbances, whereas esmolol 1.5mg/kg

together with fentanyl 2 microgram/kg was found to cause hypotension in the post intubation period. (68) We used esmolol along with low dose fentanyl 2µg/ kg in our study. The changes in heart rate and blood pressure were consistent with the study by Shailaja et al. There was a significant rise in heart rate following intubation which reached its maximum in the first post-intubation minute. We also noticed a significant fall in blood pressure with the use of esmolol bolus and infusion.

Reddy et al compared dexmedetomidine 1µg/kg over 10 minutes with esmolol bolus 2mg/kg given 3 minutes before the induction of anaesthesia in ASA I and II patients. Injection thiopentone 5mg/kg was used for induction of anaesthesia and endotracheal intubation was performed 1 minute after administration of succinyl choline 2mg/kg. They found an increase in mean arterial pressure, systolic blood pressure and diastolic blood pressure immediately following intubation.(88) In our study we used a smaller dose of esmolol bolus 1.5mg/kg with propofol as the induction agent. In terms of changes in heart rate, our study correlated with that of Reddy et al as there is an increase in heart rate following intubation. We noticed a significant fall in blood pressure following intubation which was more evident with the systolic blood pressure. This difference in our study may be due to the difference in the use of induction agent.

Our study showed a significant rise of heart rate in the post-intubation period in both esmolol bolus and esmolol infusion groups. There was no rise in blood pressure following intubation; instead there was a significant fall in systolic, diastolic and mean arterial pressure. Singh et al compared the effects of low dose esmolol 0.5mg/kg and labetolol 0.25 mg/kg in decreasing the stress response to intubation in ASA I and II

patients. They found that the hypertensive response to laryngoscopy and endotracheal intubation was not effectively reduced by low dose esmolol. But there was no associated side effects like bradycardia or hypotension.(89) In our study with administration of esmolol 1.5 mg/kg bolus, 19 out of 45 patients had hypotension in the pre-intubation period and 22 out of 45 patients had hypotension in the post-intubation period.

Singhal et al compared administration of esmolol 1.5 mg/kg at different time intervals to decrease the haemodynamic response to intubation. They concluded that esmolol bolus 1.5 mg/kg given 3 minutes prior to intubation was better than administering the drug 90 seconds or 6 minutes before laryngoscopy for attenuating the stress response. They also noticed a fall in systolic blood pressure after esmolol administration in the pre-intubation period. In our study the 1.5 mg/kg bolus dose of esmolol was administered 3 minutes prior to intubation. There was a significant fall in systolic blood pressure in the pre-intubation period after esmolol bolus administration which was consistent with the study done by Singhal et al.(90)

Miller DR et al compared the effects of esmolol 100mg with esmolol 200mg given as a bolus over 15 seconds immediately before the induction of anaesthesia. Tracheal intubation was performed one minute after administration of the muscle relaxant, succinyl choline. It was noticed that esmolol 100mg and 200mg caused a significant reduction in the post intubation increase of heart rate and systolic blood pressure although it was not completely abolished. The administration of esmolol was associated with a pre-intubation reduction in systolic blood pressure and the magnitude of reduction was higher as the dose of esmolol increases. The administration of esmolol along with fentanyl

2µg/kg was associated with better haemodynamic stability after intubation in terms of rise in heart rate and systolic blood pressure. They concluded that the administration of esmolol 100mg along with low dose narcotic fentanyl 2-3µg/kg provides better haemodynamic stability following endotracheal intubation with minimal side effects.(78) We used esmolol bolus 1.5mg/kg along with fentanyl 2µg/kg in our study. We noticed a pre-intubation significant reduction in systolic blood pressure in the esmolol bolus group. There was an increase in heart rate in the first minute which gradually stabilized over 5 minutes. The post-intubation rise in systolic blood pressure was attenuated by pretreatment with esmolol in combination with low dose fentanyl. Even though the rise in heart rate was not controlled by esmolol, there was no rise in blood pressure. These results of our study are consistent with the study done by Miller DR et al.

Feng et al in his study with esmolol 2mg/kg in ASA I and II patients noticed that esmolol could effectively decrease the rise in heart rate and systolic blood pressure following intubation. (73) In our study, though esmolol in both infusion and bolus forms prevented any post-intubation increase in systolic blood pressure, but failed to prevent the rise in heart rate following intubation. We used a lower dose of esmolol when compared to Feng et al.

Liu PL et al in his study using esmolol infusion for 12 minutes suggested that esmolol infusion according to his study settings decreased the cardiovascular responses though did not eliminate it completely. (81) We used esmolol infusion with a different dose and the duration of infusion was less, but the result obtained suggests that the cardiovascular responses are not completely suppressed by the esmolol infusion.

Rajbhandari et al studied the effects of esmolol 50mg given intravenously 3 minutes prior to laryngoscopy and its influence on the haemodynamic stress response to endotracheal intubation. He noticed that 50mg esmolol was ineffective in blunting the stress response. Patients had increase in heart rate and blood pressure after intubation.(91) We used a higher dose of esmolol bolus which failed to attenuate the heart rate response to intubation, but prevented any hypertensive response following infusion.

The study by Parnass et al comparing between a single bolus dose of esmolol 100mg and 200mg on the haemodynamic effects of endotracheal intubation when given 2.5-3 minutes prior to laryngoscopy showed that both 100mg and 200mg esmolol is effective in blunting the increase in heart rate and blood pressure following intubation.(92) In our study both the bolus dose and infusion of esmolol failed to prevent the post-intubation rise in heart rate.

Kindler et al compared the effects of esmolol 1mg/kg and esmolol 2mg/kg with and without lignocaine 1.5mg/kg on ablation of haemodynamic stress response to intubation. The study result showed that esmolol alone could reliably decrease the heart rate response but only a combination of esmolol and lignocaine decreased both the heart rate and blood pressure to intubation. (93) In our study, esmolol in both bolus and infusion forms failed to blunt the immediate increase in heart rate following intubation. There was significant reduction in blood pressure following administration of esmolol.

Ebert et al studied the efficacy of esmolol 100mg and 200mg to decrease the haemodynamic stress response to intubation given prior to induction in rapid sequence induction in ASA I and ASA II patients. They found that both the doses of esmolol

decreased the heart rate and systolic blood pressure response to intubation. They also noted a significant reduction in the systolic blood pressure in the pre-intubation period.(94) The findings are similar to those in our study except for the fact that esmolol did not decrease heart rate response to intubation. There was significant reduction in systolic blood pressure in the pre-intubation period. There was no rise in blood pressure following intubation. In our study there was a significant fall in blood pressure post-intubation in both the groups.

Sharma et al compared the efficacy of esmolol 100mg and 200mg in decreasing stress response to intubation in hypertensive patients and concluded that esmolol 100mg is better in terms of sustained decrease in blood pressure with esmolol 200mg, which would be hazardous to patients.(18) Our study had only 4 controlled hypertensives. On an individual basis esmolol bolus did not ablate the heart rate response to intubation while post-intubation blood pressure was near the base line. In the infusion group, all the 3 patients showed significant decrease in mean blood pressure. But the number of hypertensives in our study is insufficient to make a comment on the effect of esmolol on controlled hypertensives.

There were 5 diabetic patients in the study. The number is insufficient to make a conclusion about the response to esmolol. On an individual basis one patient had post-intubation tachycardia and one patient had pre-intubation hypotension.

LIMITATION

1. Although the calculated sample size was 126 patients, the study was stopped at 92 patients in order to meet the dead line for submission of thesis.

2. Among the 92 patients 3 patients were excluded from the study after obtaining consent because their baseline heart rate showed less than 60 on the day of surgery which comes under the exclusion criteria.

3. We have used non invasive blood pressure monitoring for the study. Usage of invasive arterial blood pressure monitoring would have given a more accurate beat to beat blood pressure reading.

4. Although the laryngoscopic duration was kept to less than 30 seconds, no comparison was made between the duration of laryngoscopy and the stress response.

CONCLUSION

We found in our study that both esmolol bolus and esmolol infusion reduced the hypertensive response to intubation, but the heart rate response to intubation was not effectively reduced.

There was no significant bradycardia in the pre-intubation or post-intubation period. Both esmolol bolus and esmolol infusion was associated with significant pre-intubation and post-intubation hypotension. Significant pre-intubation tachycardia was not seen in both groups. No other side effects of esmolol were noted in the study population.

We found that there is no statistically significant difference between esmolol bolus and infusion in terms of reduction in heart rate, diastolic pressure and mean arterial blood pressure. However there was a significant difference in the fall of systolic blood pressure over a period of 2 minutes pre-intubation to 5 minutes post-intubation. This difference was due to esmolol bolus causing a larger drop in systolic blood pressure during the pre-intubation period.

Based on the study results, we conclude there is no significant difference between esmolol bolus and esmolol infusion in the reduction of peri-intubation stress response. However, esmolol infusion provided better haemodynamic stability than esmolol bolus. Caution should be exercised while giving esmolol bolus at 1.5 mg /kg in patients with autonomic dysfunction, myocardial depression and uncontrolled hypertension especially when given along with drugs like propofol and inhalational agents. In the predisposed

individuals, the above mentioned drugs in combination with esmolol bolus can cause a sudden drop in systolic blood pressure after administration.

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APPENDICES

APPENDIX 1

Difficult airways were excluded from the study which are Mallampati classification more than II, short neck, obese patients, external facial and internal airway anomalies causing difficult intubation, restricted neck movements, mouth opening less than 2 fingers, buck teeth and edentulous.

Mallampatti Classification

Class I – Visualization of the soft palate, fauces, uvula, anterior and posterior pillars.

Class II - Visualization of the soft palate, fauces, uvula.

Class III - Visualization of the soft palate and base of uvula.

In Samsoon and Young's modification (1987) of the Mallampati classification a IV class was added.

Class IV – Only hard palate visible.

APPENDIX 2

American Society of Anaesthesiologists Physical Status Classification

1. Normal healthy individual

2. Mild to moderate systemic disease not limiting function.

3. Severe systemic disease, some limitation of function.

4. Incapacitating systemic disease, constant threat to life.

5. Not expected to survive more than 24 hours with or without operation.

APPENDIX 3

Variable	Infusion n=44 mean(sd)	Bolus n = 45 mean(SD)
age	36.39(11.65)	34.42(12.27)
bmi	24(3.17)	22.7(3.52)
baseline_hr	83.59(14.85)	84.4(13.51)
pre_hr1	81.55(12.94)	81.13(13.31)
pre_hr2	81.14(12.63)	81.73(11.57)
post_hr1	87.82(13.41)	89.62(12.03)
post_hr2	91.77(11.53)	90.29(10.97)
post_hr3	91.16(11.59)	90.69(13.36)
post_hr4	90.45(12.49)	88.56(13.33)
post_hr5	86.3(12.54)	86.91(11.88)
baseline_sbp	133.55(19.41)	129.49(18.78)
baseline_dbp	82.64(12.87)	77.56(10.73)
pre_sbp1	118.34(23.11)	109.44(19.74)
pre_dbp1	75(14.8)	67.38(14.01)
pre_sbp2	117.11(21.99)	104.96(20.71)
pre_dbp2	73.73(16.2)	65.31(13.43)
post_sbp1	119.3(22.02)	119.53(21.71)
post_dbp1	77.7(15.56)	74.4(16.3)
post_sbp2	120.55(23.3)	121.2(18.08)
post_dbp2	76.95(17.7)	76(14.52)
post_sbp3	117.41(21.6)	116.58(16.69)
post_dbp3	74.82(16.58)	72(11.66)
post_sbp4	116.57(20.66)	112.84(17.64)
post_dbp4	72.43(15.12)	67.89(11.75)
post_sbp5	111.8(19.56)	108.24(16.28)
post_dbp5	68.98(13.74)	64(10.02)
baseline_map	99.59(14.53)	94.96(12.69)
pre_map1	89.43(16.84)	81.29(15.59)
pre_map2	88.09(17.45)	78.29(15.42)
post_map1	91.57(17.3)	89.38(17.59)
post_map2	91.5(19.14)	91(14.98)
post_map3	88.77(17.96)	86.87(12.78)
post_map4	87.09(16.44)	82.73(13.04)
post_map5	83.16(15.18)	78.64(11.67)

BMI = Body mass index

HR = Heart rate

SBP = Systolic blood pressure

DBP = Diastolic blood pressure

MAP = Mean arterial pressure

PRE = pre-intubation

POST = post-intubation

1- first minute

2- second minute

3- third minute

4- fourth minute

5- fifth minute

Comparison of age,BMI, pre-intubation and post-intubation haemodynamic variables in Esmolol bolus and infusion groups.

INFORMATION SHEET FOR PARTICIPANT.

Dear Sir/ Madam,

You are invited to be a part of the study which aims to improve the current knowledge about a drug,Esmolol, thatblunts the increase in heart rate and blood pressure following insertion of endotracheal tube. The information in this document is meant to help you to decide whether or not to take part in this study. This study is being conducted in the department of Anaesthesiology, Christian medical college, Vellore. Please read the instructions carefully before signing the informed consent documented for participation in this study. Please feel free to ask in case of any queries or concerns.

In this study we are comparing two methods of administration of the drug Esmolol which is used to blunt the increase in heart rate and blood pressure following insertion of endotracheal tube. The methods that are being compared are: administration of the total dose of the drug over 30 seconds and administration over a period of 7 minutes.

Esmolol is a short acting drug which is already proven to blunt the unwanted responses following insertion of endotracheal tube. Both methods of administration have been proven useful and are widely accepted. We are doing this study to find out which method is better to blunt the unwanted responses following tube insertion. The expected side effects of the drug area decrease in heart rate and blood pressure which can be about 20% from your starting values. But as the drug is extremely short acting these effects do not last long and is easily treatable.

By agreeing to participate in this study you will be helping us find the best method of drug administration that blunts the increase in heart rate and blood pressure following insertion of an endotracheal tube. This study is important because these responses, although well tolerated by a healthy individual, can be hazardous in people with hypertension, thyroid disorders, history of myocardial ischemia to name a few.

The data obtained will be stored without compromising your identity and confidentiality. By signing the document, you will be allowing the research team investigators, other study personnel, institutional ethics committee and any person or agency required by law to view your data if required.

Your participation in this study is purely voluntary. If you decide not to participate in this study, it will in noway affect your medical care or your relationship with the treating doctor, the investigator or the institution. The participation in this study is purely voluntary and you have the right to withdraw from this study at any time without giving any reasons.

Thanking you for your co operation,

Dr. Ann Sumin Toms,

Principal investigator.

Contact persons for any queries.

1. Dr Ann Sumin Toms,

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Email rajsahajanandan@gmail.com

Format for Informed Consent Form for Subjects

Informed Consent form to participate in a research study

Study Title: Comparison between esmolol bolus and esmolol bolus with infusion in reducing stress response following intubation in non cardiac surgical patients

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I amfree to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

(v) I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____Signature:

Or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

PROFORMA

Comparison of Esmolol bolus against infusion to reduce peri-intubation stress response in non cardiac surgical patients

A. Infusion -1 /bolus – 2. Serial number: Date:

B. Name : Age: Sex: male -1,female -2 BMI:

Hospital number:

Associated co morbidity:

C. Vital Parameters

	HEART RATE	SYSTOLIC BP	DIASTOLIC BP	MEAN BP
BASE LINE				
PREINTUBATION				
1ST MINUTE				
2ND MINUTE				
POST INTUBATION				
1ST MINUTE				
2ND MINUTE				
3RD MINUTE				
4TH MINUTE				
5TH MINUTE				

D. **Complications**	**Pre intubation**	**Postintubation**
a. Significantbradycardia	1-yes, 0- no	1-yes, 0-no.
Management:	Atropine – 1, other drugs -2	
b. Significant hypotension:	1-yes, 0- no	1- yes, 0-no
Management:	Ephedrine -1, Phenylephrine -2 , others -3	
c. Significant tachycardia	1-yes,0-no	1-yes,0-no
Management -	fentanyl -1, Propofol -2, others -3.	
d. Significant hypertension	1-yes, 0- no	1-yes, 0-no
Management -	fentanyl -1, Propofol -2, others -3.	
e. Other complications.		

DATA SHEET

SERIAL NO	DATE	NAME	AGE IN YE/	SEX: M=1;	BMI	HOSP. NO.	CO-MORBI	INFUSION=
1	20.05.2014	SUNITA BA	33	2	24.9	856769F	0	2
2	21.05.2014	BANDARU I	39	1	22.4	907626F	1	1
3	22.05.2014	SHANTI KU	46	2	23.3	860618F	0	2
4	6.06.2014	CHANDRAS	35	1	26.1	907693F	0	1
5	11.06.2014	LOBSANG D	22	1	20.2	766659F	0	1
6	11.06.2014	VENKATESA	35	1	15.8	094549F	0	2
7	13.06.2014	SUKUMAR	55	1	22.9	786559F	0	2
8	18.06.2014	SURAJIT KU	41	1	21.6	846088F	0	1
9	17.06.2014	BRISHNA G	33	2	19.1	822504F	0	2
10	25.06.2014	GAUTHAM	40	1	28.1	876622F	0	1
11	26.06.2014	HARJAN KA	62	2	18.8	817648F	0	2
12	01.08.2014	BEENA DEV	37	2	21.5	857905F	0	1
13	01.08.2014	BANDANA (	44	2	19.2	011070G	0	1
14	04.08.2014	DEEPAK KU	28	1	21.3	828424F	0	1
15	05.08.2014	SUMATI DU	39	2	19.8	875583F	0	2
16	06.08.2014	SASHIKANT	22	1	23.7	827579F	0	2
17	06.08.2014	JULFUKAR S	40	1	22.7	886623F	0	1
18	11.08.2014	VIJAYLAKSH	44	2	28.5	874610F	0	1
19	11.08.2014	AJOY NAND	63	1	26.1	883694F	0	2
20	11.08.2014	KARTHIK	24	1	27.7	791237F	0	2
21	11.08.2014	PARIMALA	32	2	22.5	882291F	0	2
22	11.08.2014	SAKTI PADA	61	1	22.1	502427D	2	1
23	12.08.2014	INJAMAL H	20	1	18.1	775697F	0	2
24	13.08.2014	CHAKKINI P	20	2	18.7	795424F	0	1
25	14.08.2014	ANAMIKA P	41	2	27.1	047734F	0	1
26	19.08.2014	TAPAS KUM	60	1	22.2	024113G	2	1
27	19.08.2014	ARINDHAM	21	1	21.2	026413G	0	2
28	20.08.2014	KUNTI DEV	28	2	25.1	866366F	0	1
29	20.08.2014	ECHAHAK K	46	1	20.1	023938D	0	2
30	26.08.2014	SANATHAN	20	1	28.6	029333G	0	2
31	28.08.14	AVIJIT ANK	27	1	20.4	881541F	0	2
32	29.08.2014	FUZEIL AHA	43	1	20.1	693478F	0	1
33	02.09.2014	MENOKA M	41	2	21.1	843763F	0	2
34	03.09.2014	ARATAN SA	37	2	23.5	031754G	0	1
35	03.09.2014	TAPAS KUM	22	1	26.1	039762G	0	1
36	03.09.2014	WONTHAR	57	1	27.2	263941D	0	2
37	03.09.2014	VICTOR DA	43	1	24.5	647060F	0	1
38	11.09.2014	LITON KUM	26	1	28.1	898067F	1	1
39	15.09.2014	NIMA REGI	23	1	23.1	851904F	0	2
40	15.09.2014	SEENUVASA	29	1	28.7	018266G	0	1
41	18.09.2014	MASSOD A	40	1	21.7	839874F	0	2
42	18.09.2014	CHANDANA	53	2	25.3	433343F	0	1
43	26.09.2014	WASIM AN	21	1	19.3	056900G	0	1
44	26.09.2014	RABIUL DH	28	1	21.9	046698G	0	2
45	06.10.2014	RANJAN BA	40	1	18.1	241228F	0	1
46	06.10.2014	SANDHYA S	21	2	16.6	054827G	0	2

47	07.10.2014	SADAF NAZ	28	2	15.8	867072F	0	1
48	10.10.2014	BIBIN K V	32	1	21.7	003410G	0	1
49	10.10.2014	MUTHU S	31	1	25.7	408888F	0	1
50	10.10.2014	AFSAR UZZ	36	1	20.2	039926G	0	2
51	15.10.2014	SANJAY MA	26	2	22.8	854205F	0	2
52	15.10.2014	MALAY MC	31	1	17.4	851429F	0	2
53	16.10.2014	RATHIKA.J	32	2	23.4	456607D	0	2
54	16.10.2014	BABY	29	1	29.6	057275G	0	1
55	21.10.2014	MANGALA	31	2	24.9	039597G	0	1
56	21.10.2014	VIJAYAKUM	30	1	24.8	061522G	0	2
57	22.10.2014	DIPALI SAR	37	2	23.7	010451G	0	2
58	22.10.2014	ASHOK ROU	27	1	22.1	065350G	0	2
59	27.10.2014	UMA MON	41	2	24.1	616124F	0	1
60	27.10.2014	VASIHA.P.	21	2	20.8	950563A	0	1
61	27.10.2014	SEIKH SAIFU	42	1	26.3	629613D	0	1
62	27.10.2014	VENKATESA	24	1	21.6	074132G	0	2
63	31.10.2014	MUKESH BI	41	1	26.1	069768G	0	1
64	04.11.2014	BIGUN CHO	28	2	22.5	068130G	0	2
65	10.11.2014	DEV NARAY	36	1	28.9	050055G	0	2
66	12.11.2014	SUBRATA B	26	1	19.5	091294G	0	1
67	12.11.2014	HEMANT K	29	1	21.3	091413G	0	2
68	12.11.2014	RUBY DHAI	23	2	22.1	025688G	0	1
69	14.11.2014	AMBIKA	26	2	22.3	531159D	0	1
70	14.11.2014	VENKATESA	36	1	17.6	068244G	0	2
71	14.11.2014	HAKKIMA B	31	2	27.2	077724G	0	2
72	18.11.2014	SIVAKUMA	21	1	18.2	054498G	0	2
73	22.11.2014	DINESH KU	52	1	24.4	321196F	1	1
74	22.11.2014	GIRI	33	1	29.1	931334F	2	2
75	28.11.2014	AJITH KUM	30	1	27.2	051207G	0	1
76	28.11.2014	SUJAY ROY	31	1	20.1	088602G	0	2
77	02.12.2014	ABADUR RA	32	1	25.5	098273G	0	2
78	04.12.2014	REUMEGUI	23	2	19.1	027289G	0	2
79	10.12.2014	AMIT KUM.	25	1	24.5	087998G	0	1
80	12.12.2014	AMBIGA N	27	2	18.8	077454G	0	1
81	15.12.2014	DIVYA P	22	2	26.1	952435C	0	1
82	27.12.2014	RAMALEWA	42	1	28.7	937048F	0	2
83	27.12.2014	MANIACKA	70	1	26.1	937171F	1	2
84	27.12.2014	LEELAVATH	25	2	22.6	984203D	0	2
85	27.12.2014	BABU	63	1	29.1	936874F	0	1
86	28.12.2014	NAGAIAH	50	1	28.7	936862F	2	1
87	28.12.2014	MANJULA	48	2	27.3	008196F	0	2
88	28.12.2014	THIRUVIKA	42	1	23.2	104255G	0	1
89	28.12.2014	SEIKINDER	55	1	24.9	081329G	0	1
90	02.01.2015	DHANDAPA	46	1	25.4	111609G	2	2
91	22.01.2015	YUREKHA	20	2	25.5	095986B	0	1
92	22.01.2015	JEYACHANI	26	1	21.1	798202A	0	2

BASE LINE	PREINTUB/	PREINTUB/	POSTINTUI	POST INTU	POST INTU	POST INTU	POST INTU	BASE LINE
88	94	95	90	89	91	92	96	103
88	80	80	84	90	86	82	83	172
83	86	88	72	86	93	90	96	140
97	84	84	86	88	86	90	88	131
105	78	69	80	81	76	70	72	119
77	70	64	62	64	70	70	72	136
111	95	95	91	94	87	91	78	151
77	77	81	82	82	86	81	79	122
78	79	69	69	67	78	79	68	147
106	111	96	102	97	84	81	84	152
92	90	92	90	92	88	85	86	130
80	72	80	88	78	73	68	64	107
74	66	80	80	79	90	92	95	120
95	88	88	78	93	95	99	94	134
84	93	88	111	112	113	109	112	128
98	81	79	95	92	81	83	82	141
80	61	84	89	95	83	79	66	121
78	76	74	87	89	87	86	85	108
91	93	89	94	92	93	95	97	126
80	79	86	94	87	91	84	80	171
120	117	106	103	112	122	110	108	145
84	73	83	74	84	92	85	88	88
79	85	104	104	103	95	90	89	153
60	63	68	91	85	82	81	75	136
70	90	89	106	100	101	97	93	133
123	115	104	102	120	117	116	111	146
69	58	60	96	87	83	71	69	127
101	66	66	70	87	85	80	82	122
96	88	99	81	83	82	81	81	176
78	70	81	77	89	88	76	75	113
90	87	78	89	87	87	81	80	133
75	79	79	78	101	98	100	89	138
69	57	60	74	69	67	67	66	126
71	58	55	81	72	63	60	58	131
65	73	90	86	93	87	87	83	109
95	95	90	102	90	88	89	93	173
78	95	89	89	90	91	91	90	133
70	82	86	88	91	94	97	99	127
71	61	76	76	84	82	75	78	124
79	81	79	115	105	106	102	89	147
70	69	72	101	99	92	109	101	123
95	87	80	107	108	79	81	78	140
77	84	81	89	84	82	78	77	111
66	73	71	115	113	115	108	102	101

91	75	75	83	101	100	100	97	144
61	61	53	93	103	98	100	90	116
121	75	93	98	91	90	80	78	109
86	74	75	92	94	89	90	92	121
92	72	68	80	81	84	80	75	123
72	80	88	93	90	89	87	86	111
102	85	81	62	86	84	82	82	138
70	80	82	74	79	76	72	71	130
79	68	79	91	95	96	92	88	180
93	96	84	84	93	94	98	94	163
79	71	75	84	82	98	95	93	109
92	85	84	74	87	85	79	76	156
84	89	88	87	88	84	78	81	129
79	73	71	91	96	91	80	72	119
75	77	87	77	82	87	95	99	117
71	65	64	92	97	100	98	90	167
83	83	83	87	101	99	97	92	140
64	72	79	81	68	69	70	72	140
81	83	71	88	83	109	106	104	135
91	98	91	99	94	98	95	99	122
118	100	96	98	94	91	90	90	123
72	67	69	68	93	96	96	102	119
85	80	76	96	100	90	83	97	110
106	100	102	115	92	132	127	117	175
66	65	81	82	88	105	99	88	133
68	66	67	68	69	78	84	63	154
83	83	79	92	88	88	87	88	145
68	84	65	76	98	92	102	88	130
73	101	106	76	83	79	79	83	106
77	86	79	97	98	89	98	85	118
78	90	76	99	89	102	101	95	116
87	100	92	74	106	105	107	102	124
71	66	59	74	80	74	83	71	103
91	81	77	91	93	84	86	80	102
76	70	68	82	80	80	86	78	132
92	88	96	110	120	116	118	102	140
92	80	86	102	98	104	106	104	140
88	80	69	72	76	76	74	78	132
110	102	100	112	102	102	100	82	140
76	76	70	84	82	82	80	86	110
108	100	92	98	106	108	106	102	130
76	100	102	110	102	108	116	104	140
68	70	76	78	80	76	72	72	110
84	101	103	110	107	109	101	101	157
84	82	84	105	103	97	92	88	131

BASELINE [	PREINTUB/	PREINTUB/	PREINTUB/	PREINTUB/	POSTINTUI	POSTINTUI	POSTINTUI	POSTINTUI
67	115	78	113	74	75	40	72	38
96	176	100	167	96	150	93	134	77
88	111	63	110	50	76	39	98	69
82	107	79	96	72	88	62	84	60
64	92	54	88	55	95	52	90	45
79	86	58	80	52	82	52	94	66
99	140	100	144	120	155	100	156	98
65	117	70	70	50	128	88	125	84
82	138	83	128	76	116	72	113	73
73	166	88	155	77	134	74	132	70
72	128	70	128	74	130	70	128	68
68	84	54	96	71	104	70	93	63
73	106	68	95	62	92	61	83	54
78	112	71	103	65	121	89	132	91
72	114	72	129	80	116	71	110	64
96	118	80	110	76	148	100	134	93
78	111	75	115	75	161	100	156	110
66	103	59	102	62	114	66	112	65
74	90	50	94	54	118	70	100	57
88	163	89	145	99	172	110	143	84
83	79	46	82	40	109	65	125	78
58	88	57	73	46	106	81	116	83
100	111	79	132	74	106	71	146	102
81	97	68	90	63	133	100	146	104
84	112	72	105	65	127	84	121	78
98	134	91	138	91	99	64	124	89
81	107	71	95	61	162	112	143	83
80	94	47	101	51	116	71	104	57
104	155	95	159	101	115	61	116	68
75	106	71	119	76	96	72	121	83
86	98	60	75	51	82	60	104	71
83	123	82	122	79	110	81	137	87
83	124	81	103	57	124	67	99	57
77	75	47	77	51	147	92	130	88
75	78	51	71	46	126	87	126	92
108	162	111	131	81	144	96	125	76
83	116	71	117	71	109	63	127	89
73	138	86	131	70	144	85	147	90
78	86	58	88	61	103	66	104	72
83	89	50	98	60	156	112	159	101
72	124	73	118	74	94	54	94	56
87	81	47	85	45	120	78	123	79
77	93	63	91	60	97	67	93	63
65	91	55	88	55	123	87	114	78

77	116	66	110	59	119	80	130	80
72	116	69	135	64	102	67	137	96
52	128	84	106	68	113	87	126	85
69	104	60	95	60	135	90	132	85
79	109	61	96	53	133	83	128	77
81	102	67	108	72	96	63	92	55
91	109	69	112	71	120	85	137	84
87	106	72	132	86	91	60	87	56
105	108	64	116	81	153	94	145	96
71	126	75	89	58	153	94	156	83
59	105	65	108	66	116	70	120	68
88	123	78	136	78	107	73	129	83
73	86	49	86	49	105	70	98	59
68	99	63	91	56	136	89	158	108
81	89	55	97	62	95	58	110	77
117	167	109	159	115	177	116	175	114
75	134	87	113	73	124	78	131	88
90	150	94	152	92	154	88	130	80
81	121	72	118	80	101	64	96	55
81	119	82	108	71	138	97	135	95
80	111	73	100	62	98	63	97	61
74	111	69	107	68	108	69	98	60
72	112	76	119	69	95	61	117	88
102	148	107	151	91	100	54	102	60
82	129	89	146	96	118	83	118	84
100	156	99	154	105	105	70	105	52
74	109	57	96	55	128	73	114	60
78	133	83	139	87	109	62	105	63
68	92	57	105	69	95	59	119	77
73	114	77	109	75	129	99	146	109
69	116	65	114	81	119	70	127	71
77	106	63	105	58	126	86	149	100
65	96	63	97	62	100	56	86	48
62	106	66	129	73	103	59	93	51
74	110	60	102	66	128	62	140	70
88	100	60	98	64	128	76	144	86
84	110	70	108	74	146	82	146	84
80	110	70	118	70	128	68	124	70
98	120	76	110	80	117	80	114	82
70	120	60	100	60	128	62	130	70
80	100	58	102	62	120	80	124	72
87	146	88	130	80	136	84	128	88
70	94	62	88	60	110	70	110	62
107	128	87	128	76	135	92	123	87
81	100	63	97	57	128	86	114	74

POSTINTUI	POSTINTUI	POSTINTUI	POSTINTUI	POSTINTUI	POSTINTUI	BASE LINE	MAP PREIN	MAP PREIN
79	50	89	63	91	57	79	90	87
136	70	133	70	126	65	121	125	119
97	67	127	61	99	60	105	79	70
84	60	91	56	95	58	98	88	80
94	55	96	50	98	50	82	67	66
100	57	93	69	88	60	98	67	61
105	74	107	72	136	96	116	113	128
115	73	102	73	98	66	85	85	56
131	82	113	60	102	59	103	101	92
118	67	105	56	134	91	99	114	103
126	74	126	72	124	72	91	89	91
87	54	80	50	80	52	81	64	79
92	56	120	80	110	71	88	80	73
120	81	124	80	124	77	97	85	78
109	58	107	59	105	59	91	86	96
114	77	109	75	115	84	111	93	87
154	95	132	77	121	71	92	87	83
110	59	108	59	106	57	80	74	75
100	50	94	50	92	52	91	63	67
157	96	147	82	124	76	116	122	114
127	70	124	72	128	70	104	57	54
130	82	101	69	81	53	68	67	55
130	87	119	80	116	68	118	90	93
136	94	133	90	122	79	99	78	72
113	69	110	64	107	58	100	85	78
115	70	120	62	95	55	114	105	107
130	88	97	65	100	65	96	83	72
97	61	97	49	97	49	94	63	68
119	67	116	64	118	65	128	115	120
108	72	103	64	98	60	88	83	90
91	62	87	59	84	56	102	73	59
122	77	131	78	111	67	101	96	93
97	48	90	47	93	48	97	95	72
105	70	98	61	85	54	95	56	60
106	71	101	69	97	65	86	60	54
125	78	121	72	124	74	130	117	98
117	71	139	75	117	66	100	86	86
150	96	159	96	161	104	91	103	90
99	64	86	54	86	50	93	67	70
143	104	155	110	140	92	104	69	73
92	56	108	72	117	68	89	90	89
110	70	124	64	101	57	105	58	58
91	60	90	58	87	58	88	73	70
115	78	100	67	96	59	77	67	66

119	74	120	65	113	60	99	83	76
138	92	122	70	105	60	87	85	88
116	79	98	65	96	60	71	99	81
131	83	125	81	118	67	86	75	72
107	63	92	46	86	44	94	77	67
91	56	90	56	90	55	91	75	84
120	75	113	67	114	70	107	82	85
83	52	84	51	83	53	103	83	101
152	91	141	88	146	81	130	79	93
125	70	130	69	122	70	102	92	68
104	66	110	62	120	64	76	78	80
107	75	94	60	87	55	111	93	97
92	54	95	54	93	53	92	61	61
134	85	118	77	113	79	85	75	68
127	91	122	87	121	80	93	66	74
152	104	150	100	146	96	134	128	130
137	91	132	84	114	68	97	103	86
132	72	118	64	116	60	107	113	112
153	113	154	105	145	75	99	88	93
130	89	129	87	111	70	95	94	83
91	56	91	55	91	54	94	86	75
94	60	98	64	106	68	89	83	81
122	81	107	70	98	64	85	88	86
107	60	104	56	96	56	128	121	111
133	86	121	85	118	75	99	102	113
99	68	107	79	87	52	118	118	121
124	70	105	62	104	54	98	74	67
144	102	142	100	138	97	95	100	104
100	65	93	59	103	69	81	69	81
128	86	140	97	123	77	88	89	86
121	66	119	71	110	65	85	82	92
131	80	124	82	114	71	93	77	74
84	47	111	82	100	80	78	74	74
91	51	92	48	100	60	75	79	92
136	80	116	70	120	66	93	77	78
150	88	156	82	150	83	105	73	75
130	78	148	80	136	72	103	83	85
130	72	136	72	132	68	97	83	86
118	80	128	76	120	74	112	91	90
110	72	110	72	100	70	83	80	73
136	88	128	84	121	82	97	72	75
142	86	150	84	144	76	105	107	97
118	66	124	70	112	68	83	73	69
122	82	108	69	108	69	123	100	93
105	67	100	60	91	52	98	75	70

MAP POST	MAP POST	MAP POST	MAP POST	MAP POST	PRE INTUB	PREINTUBA	PREINTUBA	PREINTUBA
52	49	60	72	68	0	0	0	0
112	96	92	91	85	0	0	0	0
51	79	77	83	73	0	0	1	0
70	68	68	67	70	0	0	0	0
66	60	68	65	66	0	1	0	0
62	75	71	77	69	0	0	1	0
118	119	84	83	109	0	0	0	0
101	97	87	82	76	0	0	1	0
87	86	98	78	73	0	0	0	0
94	90	84	69	105	0	0	0	0
90	88	91	90	89	0	0	0	0
81	73	65	60	61	0	0	0	0
71	64	68	93	84	0	0	0	0
100	105	94	95	93	0	0	0	0
86	79	75	75	74	0	0	0	0
116	107	89	86	94	0	0	0	0
120	125	114	95	88	0	1	0	0
82	81	76	75	73	0	0	0	0
86	71	67	65	65	0	0	1	0
131	104	116	104	92	0	0	0	0
80	94	89	89	89	0	0	1	0
89	94	94	80	61	0	0	0	0
83	117	101	93	84	0	0	1	0
111	118	109	104	93	0	0	1	0
98	92	83	79	74	1	0	1	0
76	101	85	81	68	0	0	0	0
129	103	102	76	77	0	0	1	0
86	73	73	65	65	0	1	1	0
79	84	84	81	83	0	0	0	0
80	96	84	77	73	0	0	0	0
67	82	72	68	63	0	0	1	0
91	104	92	96	82	0	0	0	0
86	71	64	61	63	0	0	1	0
110	102	82	73	64	0	1	1	0
100	103	82	80	76	1	0	1	0
112	92	93	88	91	0	0	0	0
78	102	86	96	83	1	0	0	0
105	109	114	117	123	1	0	0	0
78	83	76	65	62	0	0	1	0
127	117	117	125	108	0	0	1	0
67	69	68	84	84	0	0	0	0
92	94	83	84	72	0	0	1	0
77	73	70	69	68	0	0	0	0
99	90	90	78	71	0	0	0	0

93	97	89	83	77	0	0	1	0
79	110	107	87	75	0	0	0	0
96	97	91	76	72	0	1	0	1
105	101	99	96	84	0	0	0	0
100	94	78	61	58	0	1	1	0
74	67	68	67	67	1	0	0	0
97	102	90	82	85	0	0	1	0
70	66	62	62	63	0	0	0	0
114	112	111	106	103	0	0	1	0
114	107	88	89	87	0	0	1	0
85	85	79	78	83	0	0	0	0
84	98	86	71	66	0	0	0	0
82	72	67	68	66	0	0	1	0
105	125	101	91	90	0	0	0	0
70	88	103	99	94	0	0	1	0
136	134	120	117	113	0	0	0	0
93	103	106	100	83	0	0	0	0
110	97	92	82	79	1	0	0	0
76	69	126	121	98	0	0	0	0
111	108	103	101	84	0	0	0	0
75	73	66	67	66	0	0	0	0
82	73	71	75	81	0	0	0	0
72	98	95	82	75	0	0	0	0
69	74	76	72	69	0	0	0	0
95	95	102	97	89	1	0	0	0
82	70	78	88	64	0	0	0	0
91	78	88	76	71	0	0	1	0
78	77	116	114	111	1	0	0	0
71	91	77	70	80	1	0	0	0
109	121	100	111	92	0	0	0	0
86	90	84	87	80	0	0	0	0
99	116	97	96	85	0	0	0	0
71	61	59	92	87	0	0	0	0
74	65	64	63	73	1	0	0	0
84	93	99	85	84	0	0	0	0
93	105	109	107	105	0	0	1	0
103	105	95	103	93	0	0	0	0
88	88	91	93	89	0	0	0	0
92	93	93	93	89	0	0	0	0
84	90	85	85	80	0	0	0	0
93	89	104	99	95	0	0	1	0
101	101	105	106	99	1	0	0	0
83	78	83	88	83	0	0	0	0
106	99	95	82	82	1	0	1	0
100	87	80	73	65	0	0	1	0

MANAGEM	POST INTU	POST INTU	POST INTU	POST INTU	MANAGEMENT OF POST INTUBATION RESPO
0	0	0	1	0	3
0	0	0	1	0	0
0	0	0	1	0	0
0	0	0	1	0	0
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0	0	0	0	0	0
0	1	0	1	0	0
0	1	0	1	0	0

)NSE: 0=NONE; 1=ATROPINE; 2=EPHEDRINE; 3=PNP; 4= FENTANYL; 5=PROPOFOL; 6= OTHER DRUGS